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The Occurrence of Pleuropneumonia-like Organisms in Material from the Postpartum Uterus: Simplified Methods for Isolation and Staining. Isabelle G. Schaub and Joseph A. Guilbeau 1

Subungual Hemorrhages and Hyperkeratoses Due to Everon. Maurice Sullivan 11

Recollections of William Stewart Halsted. A Great Surgeon. Samuel J. Crowe 15

Penicillin in the Treatment of Early Syphilis Complicating Hemophilia. Minerva S. Buerk and Harold A. Tucker 24

Studies on a Proteolytic Enzyme in Human Plasma. Oscar D. Ratnoff 29

Some Manifestations of Reflex Activity in Spinal Man With Particular Reference to the Occurrence of Extensor Spasm. Robert A. Kuhn and Martin B. Macht 43

Physiological Studies in Congenital Heart Disease. VII. Pulmonary Arterial Hypertension in Congenital Heart Disease. H. E. Griswold, R. J. Bing, J. C. Handelsman, J. A. Campbell and E. Le Brun 76

Book Reviews 89

Books Received for Review 99

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Medical
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Dr Carl V. Weller

THE OCCURRENCE OF PLEUROPNEUMONIA-LIKE ORGANISMS IN MATERIAL FROM THE POSTPARTUM UTERUS; SIMPLIFIED METHODS FOR ISOLATION AND STAINING

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The occurrence of pleuropneumonia-like organisms in the normal and pathologic vagina and cervix has been verified by the reports of a number of investigators (1, 2, 3, 4). In a recent review on the role of these bacteria in genitourinary and joint diseases, Dienes and his associates (5) conclude that "the relatively high incidence (26%) of this organism in the female genital tract suggests that it is a part of the bacterial flora in this location". The occurrence of pleuropneumonia-like organisms in the postpartum uterus, although hitherto unreported, is therefore not surprising. The primary object of this report is to describe simplified methods for the isolation and staining of these organisms. It is our intention to describe these techniques in some detail, since it has been our experience that although the literature contains excellent morphological descriptions, technical directions for the isolation and staining of these organisms are often so indefinite and incomplete or complicated that the progress of the novice in this field is seriously impeded.

In the course of a study of the effect of penicillin on the bacterial flora of the postpartum uterus (Guilbeau, Schaub and Andrews, 6) cultures were taken from the uterine cavity of 112 postpartum patients, 80 of whom had received varying amounts of penicillin and 32 of whom were untreated. Material from the uterus was obtained by means of a new technique (Guilbeau and Schaub, 7) which we have reason to believe eliminates contamination with cervical and vaginal flora.

The incidence of pleuropneumonia-like organisms in these uterine cultures is shown in Table I. These organisms were isolated from 17 of 112 cases (15.1%), in 11 of which they occured in pure culture. A marked difference will be noted in the incidence of these organisms in cultures from untreated patients and in cultures from patients who

had received penicillin. This may be explained by the fact that penicillin was demonstrated to eliminate sensitive organisms from all but 18 of the treated cases, resulting in 39 sterile specimens and 11 from which only penicillin-resistant pleuropneumonia-like organisms were isolated. In the control series of 32 untreated patients, only 2 cases were sterile, all others yielding numerous bacteria. We believe the reduction in the number of concurring bacteria in the material from patients receiving penicillin to be responsible for the larger number of pleuropneumonia-like organisms isolated from such cases, since it has been pointed out by Dienes (8) that the "demonstration of pleuropneumonia-like organisms is usually not possible in the presence of abundant bacterial growth".

TABLE I

Incidence of Pleuropneumonia-like Organisms in Cultures from the Postpartum Uterus

	ISOLATED FROM UNTREATED PATIENTS	ISOLATED FROM PATIENTS RECEIVING PENICILLIN	TOTALS
Occurred in pure culture	0	11	11
Occurred with other bacteria	1	5	6
Total number of organisms	1	16	17
Total number of cases	32	80	112
Percentage occurrence	3.1%	20.0%	15.1%

Dienes (8, 9) has reported the production in vitro of pleuropneumonia-like forms from other bacteria in the presence of penicillin. We have considered the possibility that the pleuropneumonia-like organisms isolated from patients receiving penicillin may represent variant forms of other bacteria, for example *Bacteroides*, which have been produced in vivo by the action of penicillin. However, this theory does not seem to be tenable, since all but two of the strains in our series were carried in pure culture, some for over six months, without reversion to other bacterial forms, and all were identified by stained agar preparations as recommended by Dienes (8) for the accurate morphological identification of these organisms. Culturally and morphologically all strains corresponded exactly with descriptions of pleuro-

pneumonia-like organisms published by Sabin (10) and Dienes (11), which descriptions will not be repeated here.

METHODS OF ISOLATION

The material from the uterine cavity was inoculated immediately into fluid thioglycollate medium containing 0.5% dextrose and 0.0001% resazurin. To the medium was then added 0.1 cc. of a sterile 4% solution of clarase (final concentration 0.25%) to neutralize any penicillin which might be present in the inoculum, and 2 cc. of sterile ascitic fluid (final concentration 20%) to enhance the growth of the pleuropneumonia-like organisms. The first three strains were obtained unexpectedly without enrichment of the thioglycollate medium with ascitic fluid. In these instances, after 48–72 hours incubation, the original thioglycollate cultures, which appeared to be sterile, were streaked routinely on blood agar plates and incubated aerobically and anaerobically, and from both sets of plates pleuropneumonia-like organisms were isolated in pure culture. All other strains were isolated by the following method.

The thioglycollate medium containing the material from the uterine cavity, and enriched with 20% ascitic fluid, was incubated for 24 hours. Gram stained smears from such cultures never revealed any forms which could be interpreted as representing pleuropneumonia-like organisms, nor was there gross evidence of their presence, since the original inoculum usually produced marked clouding of the medium and any slight increase in turbidity due to the growth of these organisms could not be detected. In the majority of cases the thioglycollate culture appeared to be sterile microscopically; in others only concurring bacteria, streptococci, Gram negative bacilli, etc., were seen in the smears.

After 24 hours incubation, and daily thereafter, the original thioglycollate cultures were streaked on plates of pancreatic digest agar (Brown, 12) containing 20% ascitic fluid. In preparing these plates, care was taken to use 13–14 cc. of ascitic agar to each standard petri dish, so that good agar blocks approximately 2 mm. thick could be cut from the plates for staining and transfer, as will be described later. Such plates have been used successfully, for both isolation and maintenance of stock cultures, after being stored in the refrigerator for as

long as two weeks. It has been our practice to divide the ascitic agar plates into six pie-shaped segments, using a wax pencil and marking the bottom of the petri dish accordingly. A segment was inoculated daily from the original thioglycollate culture from a specific case. Thus one week's subcultures were contained on a single plate, which could be examined rapidly for the typical colonies of pleuropneumonia-like organisms. The inoculated ascitic agar plates were incubated in a glass jar fitted with a loose glass lid, and in the bottom of the jar were placed several moist paper towels. In order to prevent the growth of molds in the jar, the paper towels should be moistened with a non-volatil disinfectant such as a benzalkonium chloride (Roccal or Zephiran). The plates were examined daily under the low power of the microscope for the presence of pleuropneumonia-like colonies, the plate being inverted on the stage of the microscope and the light reduced by lowering the condenser.

By means of the daily inoculation of ascitic agar plates, pleuropneumonia-like organisms were demonstrated to be present in the thioglycollate cultures after one to four days incubation. Eight strains were isolated after 24 hours incubation, five after 48 hours, three after 72 hours and one strain required 4 days incubation of the thioglycollate medium before growth was obtained. Because of this variation in the time required for the original growth of these organisms, daily inoculation of ascitic agar plates is recommended. No isolations were accomplished after 96 hours, but subcultures were made routinely for one week before the original thioglycollate culture was regarded as negative for pleuropneumonia-like organisms.

On 20% ascitic agar plates, growth was obtained in 24–72 hours, the majority of strains requiring two days incubation. Generally the plates appeared to be sterile macroscopically, although in a few instances tiny, pin-point colonies could be detected. Microscopic examination, however, usually revealed a heavy growth of the typical colonies of these organisms, although occassionally only a few colonies were obtained. The colonies varied in size according to their distribution on the plate, being extremely small in crowded portions, and according to the time of incubation. No difficulty was encountered in recognizing the colonies microscopically, although the medium frequently contained considerable precipitate and was milky due to the addition of a large amount of turbid ascitic fluid.

In addition to the 20% ascitic agar plates, 10% human blood, pancreatic digest agar plates were also streaked from the 24–48 hour old thioglycollate medium and incubated aerobically and anaerobically. Good growth was obtained on these plates with some strains of pleuropneumonia-like organisms. On aerobic blood agar plates nine strains grew well, five failed to grow and three were overgrown by other bacteria. Anaerobically 10 strains grew on the blood agar, four failed to grow and three were overgrown as on the aerobic plates. It is evident that blood agar plates are less satisfactory for the isolation of these organisms than the 20% ascitic agar plates, on which good growth of all strains was obtained. However, the blood agar plates, particularly those incubated anaerobically, have the advantage of producing larger colonies which can be detected macroscopically. They are very tiny, transparent, pin-point, non-hemolytic colonies. Direct microscopic examination of these colonies is difficult, but they can be studied if the lid of the petri dish is removed and the surface of the blood agar examined directly with the low power objective. The colonies appear in a different focal plane from the red cells in the medium and usually can be recognized as those of pleuropneumonia-like organisms.

STAINING OF COLONIES

Dienes (8) has emphasized that only by the examination of stained colonies can pleuropneumonia-like organisms be accurately identified. Due to the delicate nature of these organisms, stained preparations made by the usual technique of fishing colonies are useless, since they show no recognizable organisms. Klieneberger and Smiles (13) have described an agar-fixation technique which is no doubt an excellent research tool, but which is quite impractical for routine diagnostic work. The method of preparing stained agar blocks as described by Dienes (14) was found to be fairly satisfactory but to have certain limitations. In this technique, a small block of agar containing colonies is cut from the plate, placed on a slide, covered with a coverslip on which an alcoholic solution of methylene blue has been dried, and the space between the slide and coverslip filled with paraffin. We found that this method usually resulted in inadequate and uneven staining of colonies, and precipitate from the stain often spoiled the preparations. These difficulties were overcome by using the staining technique employed by Brown and Nunemaker (15), in which Way-

son's stain is applied directly to the surface of the agar. This stain gives intense staining of the pleuropneumonia-like organisms and results in clear, evenly stained colonies.

The main difficulty encountered in making these preparations, however, was in sealing the coverslip and slide with the melted paraffin. We found it almost impossible to accomplish this without moving the coverslip, and the slightest disturbance of or pressure on the coverslip results in distortion of the soft elements making up the pleuropneumonia-like colony, and colonies may be so damaged as to be almost unrecognizable. Yet in the Dienes method all preparations must be sealed by paraffin in order to support the coverslip during microscopic examination. These difficulties have been eliminated by the use of the following simple technique, which is quick, convenient and gives excellent results with no distortion of the pleuropneumonia-like colonies.

STAINING TECHNIQUE

1. Make four small balls of plasticine, approximately 2–3 mm. in diameter, and place them on a glass slide so as to form the corners of a 1 cm. square. The plasticine should be new and soft. We have found that best results are obtained by keeping the plasticine in the incubator or by warming slightly before use. These plasticine balls are to support the coverslip and fasten it to the slide, so that the pressure and slipping which causes distortion of the pleuropneumonia-like colony can be eliminated.

2. A block of agar approximately 5 mm. square is cut from an ascitic agar plate from an area suspected of containing pleuropneumonia-like organisms. It is important to choose an area containing no colonies of other bacteria, since they are usually washed over the surface of the agar when the stain is applied and obscure the colonies of pleuropneumonia-like organisms which, being imbedded in the agar are not disturbed by the spread of the stain. A thin platinum spatula, 5 mm. wide, is used to cut out the block and to transfer it to a glass slide. The agar should be approximately 2 mm. thick to facilitate handling without breaking or bending the block, and to allow easy sealing of the preparation with paraffin, as will be described.

3. The agar block is carefully lifted from the plate and gently placed

colony side up, on the slide in the center of the square formed by the plasticine balls.

4. A small, 1 mm. loop of Wayson's stain is then placed in the center of the agar block. The formula for this stain is as follows:

Dissolve 0.2 gm. of basic fuchsin and 0.75 gms. of methylene blue in 20 cc. of absolute alcohol. Add the dye solution to 200 cc. of a 5% solution of phenol in distilled water. Filter.

The intensity of the staining reaction varies with the amount of stain used in proportion to the surface area of the agar block. Larger blocks require more stain for adequate staining of colonies.

5. Place a clean coverslip over the agar block so that its four corners are supported by the balls of plasticine. The coverslip should rest slightly above the surface of the agar. Now gently press down on the coverslip, using a blunt instrument and exerting the pressure directly over the pieces of plasticine. Press down on opposite corners in rotation. In this manner the coverslip is lowered until contact is made with the surface of the agar, which is evidenced by the spread of the stain from the center to the periphery of the agar block. If the plasticine is soft and pressure is applied gently and carefully, the coverslip will not be broken, no pressure will be applied to the surface of the agar to cause colony distortion and there will be no slipping of the coverslip to damage the delicate pleuropneumonia-like organisms.

The preparation is now ready to be examined microscopically under the oil immersion objective. Care must be taken in bringing the colonies into focus, since it has been found that slight pressure of the lens, even on stained preparations, will cause distortion of the elements composing the pleuropneumonia-like colonies.

6. After the preparation has been examined and found to be satisfactory, and if it is desired to preserve the specimen, then it may be sealed with melted paraffin. We have found it convenient to keep the paraffin in a 20 cc. syringe equipped with a 19 gauge needle. The syringe and needle can be gently heated to melt the paraffin, which must be quite hot for easy handling. Gently insert the heated needle between the coverslip and slide and allow the melted paraffin to fill the space around the agar block. If the block is sufficiently thick (about 2 mm.) no difficulty will be experienced in manipulating the needle without disturbing the coverslip, which is held firmly in place

by the plasticine. It is usually necessary to fill the four sides of the square separately, since the plasticine prevents the spread of the paraffin completely around the block of agar. When the paraffin has hardened, the excess on the slide can be removed with a knife and a neat preparation results which, if completely sealed, can be preserved indefinitely in its original condition.

This staining method has given excellent results, with good differentiation of the pleomorphic elements composing the mature colony of pleuropneumonia-like organisms, and with no distortion of these elements. For routine identification purposes no troublesome sealing with paraffin is necessary and well stained preparations with intact colonies may be rapidly prepared for microscopic examination. Preparations made from ascitic agar plates are the most satisfactory, but stained blocks may also be prepared from blood agar plates. The presence of red blood cells produces a rather dark field, but the cells themselves do not interfere since they are found in a different focal plane from the pleuropneumonia-like colonies, and the intense staining achieved with Wayson's stain makes the elements composing these colonies visible against the dark background of the blood agar.

MAINTENANCE OF STOCK CULTURES

Pure cultures of the pleuropneumonia-like organisms isolated from material from the uterine cavity of postpartum patients were maintained in pancreatic digest broth containing 20% ascitic fluid or on 20% ascitic fluid pancreatic digest agar plates. Broth cultures were inoculated by cutting a small block of agar containing colonies from an ascitic or blood agar plate and transferring the agar block to the ascitic broth. Increase in the turbidity of broth cultures was never noted in positive cultures, nor could recognizable organisms be seen in Wayson-stained smears. In order to demonstrate the presence or absence of growth, it was necessary to streak the broth cultures, after 48–72 hours incubation, on ascitic agar plates on which recognizable colonies could be obtained. Broth cultures were transferred weekly and subcultures checked for growth by streaking ascitic agar plates. A number of strains were preserved for several months in this manner, but the procedure proved too time consuming and was discarded in favor of ascitic agar plates alone.

In transferring pleuropneumonia-like organisms from the original ascitic or blood agar plates to fresh ascitic agar plates, and in the continued maintenance of strains on this medium, the following technique, as described by Dienes (11) and Brown and Nunemaker (15) was used. A block of agar containing colonies was cut from the plate to be subcultured with a platinum spatula and immediately inverted on the surface of a sterile ascitic agar plate. The block of agar was then carefully pushed over the surface of the agar. The area inoculated should be confined to one half the plate, so that the distribution of colonies is restricted for easier microscopic examination. The uninoculated half of the plate may be used for the next subculture. Stock cultures of a number of strains of pleuropneumonia-like organisms have been maintained in this manner for six months. The only difficulty to be encountered was in contamination of the plates with fungi, which occurs all too frequently during incubation in the moist jars. To prevent loss of cultures through such contaminations, stock cultures should be maintained in duplicate and transferred every three to four days.

SUMMARY

Using a simple procedure based on the routine method for the isolation of bacteria in general, seventeen strains of pleuropneumonia-like organisms have been isolated from material from the postpartum uterus. The material was inoculated into thioglycollate medium containing 20% ascitic fluid and streaked after 24–48 hours incubation on aerobic and anaerobic blood agar plates. In addition 20% ascitic agar plates were inoculated daily and from these ascitic agar plates the largest number of pleuropneumonia-like organisms were isolated.

A simplified technique for staining colonies of these organisms has been described.

The significance of pleuropneumonia-like organisms in the postpartum uterus is not known at the present time. They appear to be part of the normal flora of the vagina and cervix, but Dienes et. al. (5) have presented evidence that occasionally they may have some pathogenic action in the female genital tract. In our series, the patients from whom these organisms were isolated had an uneventful clinical course, which suggests that in these cases the pleuropneumonia like organisms may be regarded as non-pathogenic.

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SUBUNGUAL HEMORRHAGES AND HYPERKERATOSES DUE TO EVERON

MAURICE SULLIVAN

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Fingernail polish is well known as a cause of allergic contact dermatitis. (1) In persons hypersensitive to one or more of the ingredients of nail polish, plaques of erythematous, edematous, scaly dermatitis may be observed on the eyelids, chin, sides of the neck, cheeks thighs or any other areas of the skin readily reached by and frequently in contact with the fingernails. Fingernail polish dermatitis never occurs on the fingers nor is there evidence of acute inflammation of the nails; it is, therefore, an example of a finger borne contact dermatitis with a diagnostic distribution in telltale areas remote from the application site. No one ingredient has been implicated as the cause of every case of nail polish dermatitis. The platicizers, fixatives, dyes and perfumes separately or in combination have been incriminated.

At the Round Table Discussion of the 1948 meeting of the American Dermatological Association, several members from different sections of the United States reported a new entity affecting the fingernails; it is caused by the application of nail bases. These are cosmetic preparations which are applied to the surface of the nail prior to the application of the lacquer to insure the adherence of the lacquer. Cases were reported from New York City by Sulzberger, Sharlit and Rein, from Chicago by Mitchell, and from Los Angeles by Ayares. The widespread use of nail bases makes it imperative to disseminate rapidly information regarding this new entity, as it can be confused with onychomycosis, psoriasis, verrucae and other subungual tumors, results of trauma to the nail bed, and a manifestation of blood dyscrasia. If the condition remains unrecognized the patient is likely to continue the use of the nail base in an effort to cover up the unsightly appearance of the nails and thus further aggravate the condition. In severe cases there is often excruciating pain, and surgical removal of the nails is necessary in some instances. The following case due to a nail base, Everon, is reported because it is illustrative and corresponds to the description of other cases reported at the A.D.A. Round Table.

CASE REPORT

Mrs. R. E. White, aged 42, consulted me on 18 May 1948 with the complaint of discoloration and deformity of the fingernails and pain in the finger tips. There was no history of skin diseases in the past. Her general health was excellent. For many years she had used and tolerated Revlon nail polish. On the morning of 5 March 1948 a beauty parlor operator applied Everon for the first time. This base

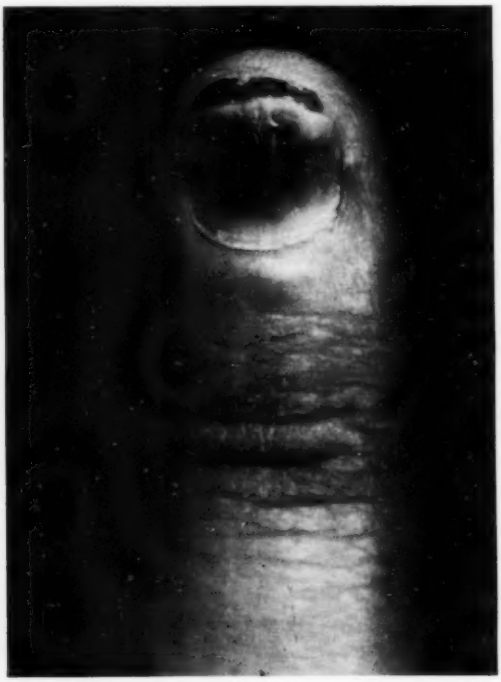

FIG. 1.

was then covered in the usual manner with Revlon nail polish. That night, according to the patient, she experienced a painful sensation under one fingernail. She attached no significance to the pain and one week later she returned to the beauty parlor, where another application of Everon was made. Again Revlon was applied on top of the nail base. That night and for several days thereafter she experienced increasing pain under all of the nails and when she finally removed the nail polish she noted a purple-brown discoloration under all of the nails. Above the

discolored area, beneath the nail, a lighter brown material had accumulated. This material grew upward and pushed itself above the edge of the nail. She consulted several physicians who were not acquainted with the condition and it was their concensus that she had onychomycosis. Many scrapings of the material beneath the nails and cultures on Sabouraud's medium failed to support the diagnosis, and treatment for fungus infection of the nails was ineffective. She consulted me nine weeks after the onset.

Examination: The fingernails were universally involved by a process (See Figure I) consisting of onycholysis of the upper half of each nail, thick hyperkeratoses (See Figure 2) of the nail bed under the area of onycholysis and wide

FIG. 2.

bands of brown discoloration across the middle and lower portion of each nail. Punctate hemorrhages were present on the borders of the bands. There was slight edema of the terminal phalanx of each digit.

Patch tests with Revlon and Everon were performed on 18 May 1948. There was no reaction to Revlon, but there was a markedly positive 48 hour reaction to Everon, consisting of a plaque of erythematous, edematous, vesicular inflammation which persisted until 10 June 1948.

On 17 June 1948 patch tests were performed with three other brands of nail bases, namely, Foolpruf, Stazon and Perma-Nail, and with three ingredients of Everon, namely, methyethyl ketone, a rubber solution and a resin solution. Markedly positive 48 hour reactions were produced by the three other brands and by the rubber solution.

Treatment: The patient was apprized of the nature of the disease so that she would avoid further application of Everon or other nail bases. Compresses of

saturated solution of boric acid applied with one inch roller bandages under rubber finger cots were advised. After the compresses had been in place for one hour and there was softening and maceration of the hyperkeratotic material it was possible to cut away a small amount of the protruding hyperkeratosis and to trim the nails. With this simple treatment there was symptomatic relief and in five weeks there was considerable improvement. The brown bands had grown upward and the hyperkeratotic material had been appreciably reduced. The texture of the nails, although longitudinally ridged, was approximately normal.

DISCUSSION

When this disease was called to the attention of the American Dermatological Association many of the members commented that they had observed patients with a similar condition but had failed to recognize it. It is likely that many reports of subungual hemorrhages and hyperkeratoses will soon appear. It is probable that the nail bases, when applied, are not precisely confined to the outside of the nail and that small quantities of the liquid spill behind the nail and gain access to the under surface. This condition differs considerably from nail polish dermatitis, in that inflammation at remote finger born sites is not observed. It is likely that the protection of the overlying nail lacquer prevents the nail base from causing inflammation to the eyelids, chin, neck and the sites characteristically implicated by nail polish. In an individual hypersensitive to nail polish, however, it would be possible to have a combination effect. Mitchell of Chicago is preparing an exhibit on the subject for the forthcoming American Medical Association Meeting. Through this medium many physicians will become acquainted with the entity and will save unnecessary discomfort and suffering.

SUMMARY

The case of a patient with subungual hyperkeratoses and hemorrhages due to Everon is presented.

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RECOLLECTIONS OF WILLIAM STEWART HALSTED*

A Great Surgeon

S. J. CROWE

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My father was born on a farm in Washington County, Virginia. He received a college education and went to the College of Physicians and Surgeons in New York, was an interne in Bellevue and attended Dr. Welch's lectures. He never knew either Dr. Welch or Dr. Halsted intimately, but was much impressed with the new medicine these two men had brought from Europe. On account of my mother's health he moved to Atlanta. The South was impoverished, and he had to work very hard to make a living, doing everything—general practice, obstetrics, and some surgery. As I grew up my impression of medicine was that it was a most undesirable profession. My father was always tired, pale and thin. He was often called out at night on obstetrical cases. I never knew him to take a vacation—and the summers are very long and hot in Georgia. Medicine was the one profession I never wanted to enter.

At the University of Georgia, the Professor of Physics interested me in the future of electricity and I was determined to become an electrical engineer. My father's one idea was that I should study medicine, return to Atlanta and gradually take over his practice. I never discussed my ambitions with him, but all my activities at the University were devoted to athletics and courses that would enable me to enter the Georgia Tech. No more biology or premedical work was taken than was absolutely necessary for me to get an A.B. degree. My father knew nothing of this. It never entered his head that I would not become a doctor. After graduation I realized for the first time how much he wanted me to study medicine. In that conversation I heard of the Johns Hopkins Medical School for the first time. His chief desire in life was that I should go to Baltimore and come under the influence of Dr. Welch, Dr. Osler and Dr. Halsted. I could not refuse.

How I got into the Hopkins Medical School I will never know. I

*Read at a meeting of the Surgical Staff of the Johns Hopkins Hospital in May 1948.

came to Baltimore in 1904 much against my will and with no interest in medicine. In some way I managed to pass at the end of the first year. During the summer following my graduation at the University of Georgia, I had joined two friends on a camping trip in the North Carolina mountains. We hired a covered wagon and a team of horses and drove aimlessly through the mountains toward Asheville—with no maps or guides. We slept in the wagon and tied the horses to trees. It rains in those mountains almost every day, but there were no mishaps and the six weeks trip was a great success. As soon as my first year in the medical school came to an end I gave a great sigh of relief and hurried to Georgia to organize another camping trip in the North Carolina mountains. This was an unusually cold and rainy summer, but we reached Highlands, North Carolina, stayed in that lovely country a few days, letting the horses graze, then moved on in the general direction of Asheville. After an unusually cold rainy night I got up the next morning to feed the horses and found that one of them—a big Percheron—was standing with his front legs far apart and his head hanging. He was as stiff in every joint as if he had been made of wood. I was amazed. On my grandfather's farm in Virginia I had seen horses turned out to graze in any kind of weather. I thought they were as immune to weather as a tree, so of course had brought along no horse blankets. I was also much disturbed to be in this wild country, so far from home, with a hired wagon and two valuable horses and one of them sick. Without waiting for breakfast, a shave or a wash up, I got on the well horse and leading the other at a snail's pace went down the road in search of a cabin, a barn, and some advice about what to do for a stiff horse. I met no one, but finally came to a side road and saw a cabin in the distance. An old mountaineer was sitting on the porch, so I told him my trouble and asked where I could find a barn for my horse. His horse was about the size of a donkey and his barn about the size of a large chicken coop. He said all other barns in that part of the country were about the same size. I was truly in despair, but after a lot of useless talk he finally said "Doc" Halsted from Baltimore lived about two miles up the road, that he had horses and a big barn with real box stalls.

I mounted the good horse, leaving the stiff one standing in the road and soon came in sight of the big barn, a beautiful, well kept lawn, and

about half an acre of the most georgeous dahlias I had ever seen. There were two small houses. I knocked at the door of one, and finally a maid in dainty white cap and uniform appeared. She said Dr. Halsted was out on the place somewhere. I sat on the porch for about an hour. Then Dr. Halsted came out of the house in spotless flannel trousers, patent leather pumps and a white silk shirt. I was much embarrassed because I knew I looked like a tramp and I certainly felt like one. I told him I had just finished the first year at the Johns Hopkins Medical School, was on a camping trip, and about the stiff horse. Instead of saying "go get your horse and put him in my barn", he called a man, had his buggy sent around, and insisted that we drive down and look at the sick horse. That impressed me as being very kind, but I was amazed at what happened after we got to the horse. Dr. Halsted got out, walked through the mud in his fine clothes, walked all around the horse, feeling every muscle and joint. Then standing in the middle of the road he asked me to lead the horse. We made slow progress for about fifty feet and returned. This was repeated several times. Dr. Halsted was intensely interested and finally said he did not think it was hip-joint disease, but probably muscular rheumatism. At his suggestion I tied the horse to the back of the buggy and we literally crept up the road. On the way Dr. Halsted said he thought the horse should be bandaged with oiled silk after a rub down with Sloan's liniment. He had the horse put in a box stall with a lot of straw, gave me some lunch, and I rode off to the country store where I bought all the liniment and oilcloth in the store. The oilcloth such as is used to cover kitchen tables was of all colors, since it took all they had in the store to bandage such a big horse. I bandaged him from his ears to his hoofs. He recovered completely.

I was there a week, but was much embarrassed because I had no fine clothes. I talked very little, but Dr. Halsted seemed to like me, and finally I told him my ideas of medicine as a career. He said very little then, but during the days that followed he talked more and more about medicine being a living, growing, constantly changing and most fascinating study. That of course the doctor must know the structure and the physiology of the various organs and how to treat the sick, but that also it was the duty and function of the doctor to seek by clinical and laboratory research to lessen in the next generation the number of

cripples from disease that constantly flow into our hospitals. That there was a great satisfaction in restoring a sick person to health, but that there was greater satisfaction if a man was fortunate enough to devise some means to prevent disease. That monetary rewards were necessary or advisable only to the extent of allowing the doctor to care for his family, to travel in order to acquire new ideas, and to have the leisure and peace of mind to think and read and try to add something during his lifetime of lasting value to medicine. This was in 1905. No doubt it was for these reasons that he enthusiastically welcomed the Full Time Plan when it came along in 1913.

That chance meeting in the mountains with Dr. Halsted changed my whole life. Without it I am sure I would have withdrawn or have been asked to withdraw from the medical school during the second year, because I was not interested, and I was not interested because I didn't understand what opportunities medicine offered for a happy as well as a useful life. I have gone into some detail with this story, because all of you may have an opportunity to help some young man in the same way.

You can learn from Dr. MacCallum's biography of Dr. Halsted that the Halsted family in New York was prominent financially and active in various philanthropic projects. Dr. Halsted entered Yale at the age of eighteen. His scholastic record was poor. There is no record in the Yale Library that he ever borrowed any books. He spent most of his time in athletics—rowing, baseball, gymnastics, and in his senior year was captain of the Yale football team and made the winning goal in the game with Eaton, which Yale won two to one. He entered the College of Physicians and Surgeons in New York and became intensely interested in anatomy. He graduated with honors in 1877, and received an appointment at both Bellevue and the New York Hospital. He spent the next two years in Europe attending courses in anatomy and the clinics of Billroth, Mikulicz, Von Bergmann, Thiersch, Von Volkmann and others, watching the development of Lister's antiseptic surgery in Germany. On his return to New York in 1880, he worked with Dr. Welch in pathology at Bellevue, inaugurated at the Roosevelt Hospital the first surgical out-patient department in New York, was demonstrator of anatomy in the College of Physicians and Surgeons, visiting physician to Bellevue, The Presbyterian Hospital and the Charity Hospital on Blackwell's island, and Surgeon-in-Chief to the

Emigrant Hospital on Ward's island. In addition, he carried on a quiz course at his house on 25th street, and for several years had sixty-five or more students taking the course. These many and varied activities attest to his enthusiasm and splendid physical health.

It was at this time he became interested in Koller's discovery that the cornea could be anesthetized with cocaine. He experimented on himself and found that by injecting this drug into a sensory nerve he could render the whole area from which its branches came insensitive to pain. Nearly forty years later at a great banquet at the Belvedere Hotel in Baltimore he was awarded a gold medal by the National Dental Association in recognition of his discovery of local anesthesia and his great service to dentistry.

When Dr. Halsted was making these experiments on himself in 1885, it was not known that cocaine was a demoralizing, habit-forming drug. Through the aid and encouragement of Dr. Welch he finally overcame it, but this accident radically changed his whole life. He returned to New York after a cure in a Providence Hospital to a more thoughtful and leisurely life, with time for reflection and study of the surgical problems that interested him most, a life far more fruitful than it could ever have been if he had continued the strenuous pace he had set for himself in the beginning.

The Johns Hopkins Hospital was opened in May 1889. Dr. Welch had accepted the appointment as Professor of Pathology in 1884. In 1886 he invited Dr. Halsted to come to Baltimore. He lived with Dr. Welch at 506 Cathedral Street and in the Pathological laboratory began experimental studies that continued without interruption as long as he lived. It was then that he and Dr. Mall did their fundamental work on intestinal suture, and during the following year Dr. Halsted began his experimental studies of the thyroid in dogs. At this time Dr. Halsted also began to work experimentally on animals on the basic questions of operative procedures and the healing of wounds. He showed that cultures after the most meticulous use of Lister's methods still showed the presence of bacteria. He made histologic studies of healing wounds and of tissue reaction to various types of suture material. These laborious and careful studies led him to the realization of the great importance of the careful handling of tissues, the necessity of controlling bleeding with the minimum of crushing of tissues with forceps, and

the value of transfixing vessels and ligating them with the smallest and finest silk. Also the value of exact approximation of tissues and avoidance of dead space in the healing of wounds.

These years of laboratory work were largely responsible for Dr. Halsted's appointment in October 1889 as Associate Professor of Surgery and Acting Surgeon to the Hospital. He was not made Professor of Surgery until April 1892. He was then 40 years of age. His work during the six years he had been in Baltimore and his University appointment show how completely he had overcome the cocaine habit. Also his work during these six years, and indeed throughout the remainder of his life, illustrates one of Dr. Halsted's most prominent characteristics: i.e., his ability to select a basic problem and to stick to that problem until it was solved to his satisfaction. Dr. Dandy had the same gift. It was one of the outstanding characteristics of these two men that won for them respect and fame, and one that all young men should emulate.

In Baltimore, Dr. Halsted never gave a systematic course of lectures. His clinics and ward rounds were meant to present some fundamental underlying principle of disease and the surgical treatment of disease in a way that would stir the spirit of an investigator. He taught by example more than by text.

It was my privilege to see much of Doctor and Mrs. Halsted in their home at 1201 Eutaw Place. His house was filled with the most beautiful antique furniture and rugs. A wood fire always burned in his study. He rarely read anything but medical articles and books dealing with some subject on which he was working. When writing his paper on "The Operative Story of Goitre" in 1919, he read hundreds of papers bearing on the subject. No reference was ever quoted until he has seen the original article. His table was covered with dictionaries and grammars in every language and boxes of books from the Surgeon General's library were constantly arriving.

When he and Mrs. Halsted had guests to dinner, it was the Professor who selected the menu, the china, the wine, and even the table linen. I was much impressed late one afternoon to find him in the dining room supervising the ironing of the table cloth after it had been spread on the table. All folds and creases had to be removed. On another day I found him bandaging with the greatest care the leg of a large plush

tiger that he had bought for the five year old son of one of his friends. On the day before the child had fallen and badly skinned his knee.

About 1919, he began to have gall stone colic for which a few weeks later he was operated on by Dr. Follis. For several days he had complained to Dr. Welch of pain, but did not localize it or suggest a cause. Then one evening when he and Dr. Welch were walking up the steps of the Maryland Club, Dr. Halsted stopped and, looking very serious and distressed, said "Welch I have found the cause for my pain. It's an aneurism. Put your hand under my vest and see if you don't think I am right." Dr. Welch was amazed to feel the violent, rhythmical pulsations, and became much excited. Dr. Halsted had spent many hours in having a thin rubber bag made, which he had fastened to his chest wall with adhesive. From the bag a small rubber tube ran to his pants pocket where it ended in a bulb. While Dr. Welch was still palpating the aneurism Dr. Halsted gave a great squeeze to the bulb and the bag exploded with a bang.

I well remember a few days before Christmas, Dr. Halsted came home with about ten pairs of green and yellow carpet slippers that he had bought on Gay Street. He wrapped each pair of slippers in many layers of tissue paper, placed them in a Christmassy-looking box and directed the boxes to Dr. Thayer, Dr. Finney, Dr. Bloodgood, Dr. Young, Dr. Welch and others. On each box was pasted a cancelled English, French, German, Austrian or Italian stamp that Dr. Halsted had saved for this purpose, and in each box was placed the visiting card of some foreign doctor who had visited the Hopkins Hospital. On each card was written in English, French, German or Italian "The Season's Greetings."

I have told you how my sense of loyalty and my love and admiration for my father forced me to go to the medical school in 1904 against my wishes. The same sense of loyalty, love and admiration for Dr. Halsted diverted me eight years later from my chosen specialty, neurological surgery, into a branch of surgery about which I knew absolutely nothing and at that time regarded as the lowest form of all surgery—otolaryngology.

From the time he became Professor of Surgery, Dr. Halsted limited his operative work to the maladies that interested him most: fracture of the neck of the femur, intestinal anastomosis, hernia, cancer of the

breast, thyroid and parathyroid diseases, surgery of the gall ducts and vascular surgery. This was a deliberate plan in order to give his house officers better training, and to give himself more leisure to think, to read and to carry on investigations. The period of training for house officers was long—from 12 to 14 years. As their knowledge of disease in all its manifestations increased, their responsibilities became greater. The Resident Surgeon during the early years of the hospital could do and did do approximately 90 per cent of all the operations. As suitable men appeared, Dr. Halsted encouraged them to interest themselves in some special branch of surgery. Thus, in a gradual and unhurried way, the departments of neurological surgery, genito-urinary surgery, orthopedics, and otolaryngology were built up. Of the men selected to head these various departments, only Dr. Cushing was kept in line and advanced until he became Resident in Surgery. The others were diverted into special branches after they had been in training long enough to master some of the fundamentals of general surgery.

All my training had been in the Hunterian Laboratory and in the hospital as Resident in Neurological Surgery. Dr. Cushing had invited me to go to Boston with him, when without any warning Dr. Halsted one day asked me to stay on and try to build up a department of otolaryngology. The fact that I had never seen a tonsillectomy, a mastoidectomy or the inside of the nose did not disturb him. He simply said the regional anatomy, physiology, pathology and the technical procedures of treatment could soon be learned. In the next two years I went abroad frequently for a month at a time for intensive study of some phase of this specialty, but always at my own expense. Then came the first World War, and I was on my own. This may have been the reason, but at any rate from 1914 to 1924 my enthusiasm for my specialty did not grow and my knowledge of otolaryngology was far from satisfactory to me, and I suspect to Dr. Halsted also. I spent all of my spare time during those years working in the Hunterian Laboratory on the pituitary gland, on the function of the adrenals with Dr. Wislocki, who is now Professor of Anatomy at Harvard, in removing the thymus gland from innumerable newborn kittens for Dr. Park, and on lung abscess with Dr. Scarff. Dr. Halsted, however, never criticized or made any suggestions. He was always interested, cordial and encouraging. He would occasionally come into

the operating room and look over my shoulder when I was doing a tonsil or mastoid operation. He never lived to see the awakening of my interest in otolaryngology that came with the advent of the audiometer, the establishment of the Otological Research Laboratory and a sane method for learning something about the ear and how it functions.

In concluding this talk I wish to say, in agreement with Dr. MacCallum, that Dr. Halsted's greatest accomplishment lay in the establishment of a school of surgeons, who in turn have passed on to their assistants his spirit of inquiry and desire to learn the cause of disease, his teachings regarding the delicate handling of tissues, hemostasis and asepsis, and his unfailing courtesy and interest in the patient as a human being.

PENICILLIN IN THE TREATMENT OF EARLY SYPHILIS COMPLICATING HEMOPHILIA*

Report of a Case Treated with 48 Million Units of Oral Penicillin G

MINERVA S. BUERK AND HAROLD A. TUCKER

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An unusual therapeutic problem recently arose in the Syphilis Clinic of The Johns Hopkins Hospital when a patient with hemophilia was found to have untreated early syphilis. Because of his grave hemorrhagic disease, it was believed that parenteral arsenobismuth or penicillin therapy was inadvisable. Although oral penicillin has been considered unsuitable for general syphilotherapy (1), in our opinion the oral route of penicillin administration in the case here reported provided the least objectionable method of treatment at present available.

CASE REPORT

The patient (J. H. H. 291036) was a 22 year old Negro with known hemophilia, first seen in the Syphilis Clinic of The Johns Hopkins Hospital in March, 1948 as a sexual contact of a patient with gonorrhea. No clinical or bacteriologic evidence of gonococcal infection was found, but repeated serologic tests for syphilis were positive with titers as high as 64 Eagle units. He stated he had had transitory sore throat and "blisters" on his penis one month before. Although a lumbar puncture would have permitted a more explicit diagnosis (i.e., early latent or early asymptomatic neurosyphilis), the procedure carried with it certain risks in this particular case and the examination was foregone. Because of the hemophilia it was decided that oral penicillin therapy was the treatment of choice and the patient was admitted to the ward for syphilotherapy and study.

The maternal grandfather, a white man, and four of the patient's brothers also had hemophilia. Three of the six male siblings had died from hemorrhage at 18, 22 and 37 years of age; the other brother with hemophilia died of poisoning when he was 24 years old. There was no other known syphilitic disease in the family.

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* From the United States Public Health Service and the Johns Hopkins University Venereal Disease Research and Post-Graduate Training Center, Baltimore 5, Md. The laboratory studies were carried out in the Laboratory of Experimental Therapeutics, School of Hygiene and Public Health, Dr. Harry Eagle, Director.

Since early childhood, the patient had been hospitalized elsewhere on 19 occasions for hemorrhagic episodes of variable severity. In April 1943 and March 1947, he had been admitted to the wards of the Johns Hopkins Hospital because of massive hematomas and hemarthroses. On these admissions he was studied thoroughly from the hematologic standpoint and serologic tests for syphilis were negative.

On physical examination, at the time of the March 1948 admission, the patient was found to be well nourished and developed; he weighed 71.7 kg. The skin and mucous membranes were not remarkable. The posterior cervical, axillary and epitrochlear lymph nodes were enlarged bilaterally, but these, as well as the enlarged right inguinal nodes, were not fluctuant or tender. The blood pressure was 120 mm. of mercury systolic, 76 mm. diastolic. The heart was normal to percussion and auscultation. The liver extended five cm. below the right costal margin on deep inspiration and was firm and nontender. No active lesions or scars were seen on the genitals. There was enlargement of the weight-bearing joints and of the left elbow, with varying degrees of functional impairment. A massive, partially calcified hematoma could be palpated in the anterior aspect of the left thigh. Neurologic findings were normal.

Numerous laboratory studies were carried out. Blood counts, hematologic indices and platelet counts were normal. The non-protein nitrogen, fasting blood glucose, cholesterol, total serum proteins and albumin-globulin ratio, serum calcium and alkaline phosphatase activity were all within the range of normal. The bleeding time was three minutes. The prothrombin time was 19 seconds, which was normal for the method used. The venous clotting time at 37°C. was 15 minutes in the first tube, 20 and 33 minutes in the second and third tubes respectively. The Rumpel-Leede test was negative. Five serologic tests for syphilis varied in titer from 24 to 64 Eagle units. Radiographic examination of all the large joints revealed changes characteristic of old hemorrhagic arthropathies.

Throughout his stay in the hospital the patient was given a regular house diet and fluids as desired. The oral penicillin preparation employed was in the form of compressed tablets, each containing 100,000 Oxford units of crystalline sodium penicillin G, with 0.5 gm. of trisodium citrate incorporated as an antacid buffer.[1] He received a total dosage of 48 million units, 500,000 units (five tablets) every two hours for a period of eight days. Meals were given midway between doses of penicillin.

No untoward reactions occurred during or after the course of treatment. Rectal temperatures taken every two hours through the first 24 hours of therapy did not show evidence of a febrile Jarisch-Herxheimer reaction. During the period of treatment, serial examinations showed no significant alterations in the hematologic findings (2). Seventy-four days after the start of penicillin therapy the patient

[1] The oral penicillin G used in this study was furnished through the courtesy of E. R. Squibb and Sons.

was clinically well from the standpoint of his syphilis and no new clinical manifestations of hemophilia had appeared. The serologic titer was 16 Eagle units.

Special penicillin studies were carried out on this patient. Blood specimens were taken by venepuncture one half, one, two, three, four, eight, 12 and 24 hours after the first dose of oral penicillin. Thereafter, throughout the course of therapy, daily specimens were drawn one hour after breakfast and immediately prior to the next dose of penicillin, with the exception of the ones taken at 168 and 192 hours; breakfast was omitted before these venepunctures. Pooled urine specimens

TABLE I

Penicillin Serum Concentrations and Total Urinary Recovery During Administration of Oral Penicillin G

	TIME IN HOURS							
	½	1	2	3	4	8	12	24
Serum*								
Oxford Units	0.42	5.03	0.64	2.19	0.32	0.32	0.42	1.71
Micrograms	0.25	3.01	0.38	1.31	0.19	0.19	0.25	1.02
Urine†								
Oxford Units	4,510	51,600	80,200	53,500	47,400	72,400	112,000	405,000
Micrograms	2,700	30,900	48,000	32,000	28,350	43,300	67,000	242,000
	48	72	96	120	144	168‡	192‡	
Serum*								
Oxford Units	1.06	0.30	0.95	1.29	1.20	4.01	6.02	
Micrograms	0.63	0.18	0.57	0.77	0.72	2.40	3.60	
Urine†								
Oxford Units	441,000	638,000						
Micrograms	264,000	382,000						

* Penicillin concentration in units and micrograms of penicillin G per cc. of serum.

† Penicillin concentration in total pooled urinary output for period ending at time stated (total volume in cc. × concentration per cc.)

‡ Patient chewed the 30 penicillin tablets making up the 6 doses prior to fasting venepuncture.

for the corresponding intervals of time were collected during the first three days of treatment. These serum and urine specimens were assayed by one of us (H.A.T.) for penicillin G content using the Eagle modification of the Kirby-Rantz method[3]. The endpoint in this serial dilution technic of penicillin assay was the complete inhibition of hemolysis of human group O erythrocytes by the C-203 strain of *Streptococcus pyogenes* following incubation for six hours at 37°C. and then ten to 12 hours more at room temperature.

RESULTS

In Table I are shown the penicillin G concentrations per cc. of serum at the various time periods after the start of treatment. The mean concentrations of penicillin in the pooled urine specimens multiplied

by the total volume of urine excreted in a given interval are also tabulated for the first 72 hours. These values are expressed both in Oxford units and in micrograms of penicillin G.

All serum assays showed concentrations of penicillin G in excess of 0.30 Oxford units per cc. The post-prandial morning specimens (after the first day) ranged from 0.302 to 1.71 units per cc. of serum and were equivalent to levels obtained after the intramuscular administration of approximately 100,000 to 330,000 units of penicillin G in aqueous solution at intervals of two hours in the average adult (4). These data confirmed numerous reports in the literature to the effect that effective plasma levels may be maintained by the use of oral penicillin, but that approximately five times as much penicillin must be given orally as is necessary parenterally in order to maintain a given plasma concentration (5–9). The total penicillin G recovered in the three 24-hour pooled urine specimens was approximately eight per cent of the daily dosage (6,000,000 units); this likewise resembled results reported by others (6, 8).

SUMMARY

Buffered crystalline sodium penicillin G was used for the treatment of early syphilis in a patient with hemophilia. A total of 48 million Oxford units was given in eight days (500,000 units every two hours), and serum and urine assays were carried out during treatment. The plasma concentrations corresponded to those in patients given 100,000 or more units in aqueous solution every two hours by the intramuscular route. By present standards, this probably represents adequate therapy for early acquired syphilis.

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STUDIES ON A PROTEOLYTIC ENZYME IN HUMAN PLASMA

IV. The Rate of Lysis of Plasma Clots in Normal and Diseased Individuals, with Particular Reference to Hepatic Disease[1]

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In 1914, Goodpasture (1) observed that the clotted blood of four patients with atrophic cirrhosis of the liver dissolved within 16 hours when incubated at 37°C. On the contrary, the blood clots of normal persons did not lyse for many days. Since then, this phenomenon of fibrinolysis has been described under a wide variety of conditions. In an attempt to evaluate its clinical significance, the fibrinolysis of plasma clots has been measured in normal persons and in patients with a wide variety of diseases. Data will be presented which indicate that, under certain specified conditions, rapid fibrinolysis is particularly frequent in patients with hepatic disease, although it may occasionally be present under other conditions as well.

METHOD

Venous blood was drawn under sterile conditions from the antecubital vein of human subjects and transferred to a 50 cc. centrifuge tube containing 0.2 cc. of oxalate mixture for each 5 cc. of blood added. The oxalate mixture was prepared by dissolving 3 grams of ammonium oxalate and 2 grams of potassium oxalate in 250 cc. of water (2). The blood was centrifuged immediately for 20 minutes at 2000 r.p.m. in an angle centrifuge (rim diameter 10 inches) and the plasma separated. Half a cc. of plasma was placed in a sterile Wassermann tube 13 mm. in diameter and the plasma recalcified with 0.1 cc. of sterile M/20 calcium chloride solution. The tube was then closed with a sterile rubber stopper, incubated at 37°C., and observed several times daily for clot lysis. Grossly, the process of clot lysis appeared to begin when the clot lost its firm appearance and seemed friable. In the course of

[1] These studies were conducted under contract with the Office of Naval Research, U. S. Navy.

several hours the clot appeared to melt, usually from the top down, until only a cloudy suspension remained. The contents of the tube

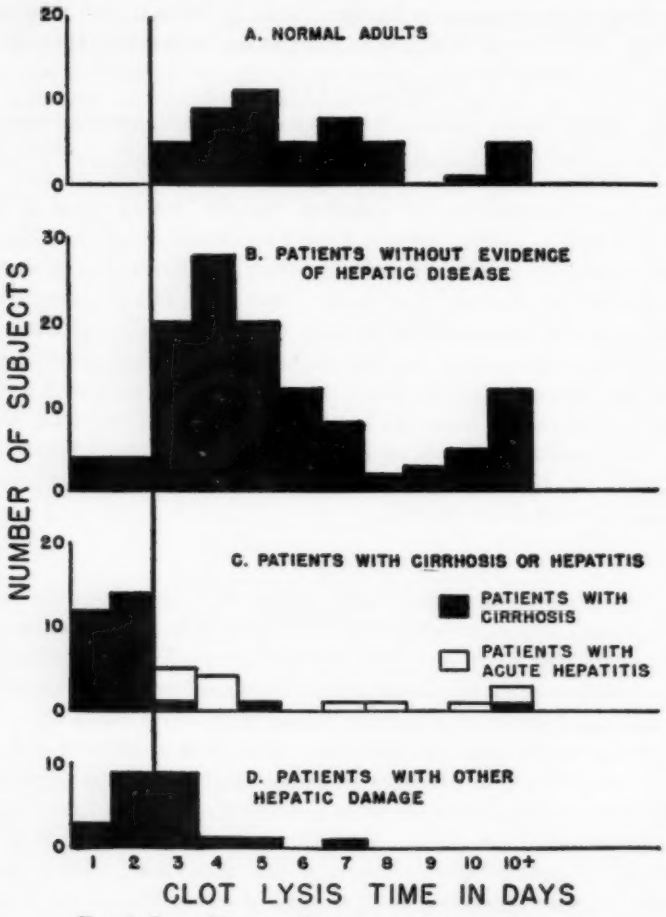

FIG. 1. LYSIS TIME OF RECALCIFIED PLASMA CLOTS IN NORMAL AND DISEASED INDIVIDUALS.

gradually became clear and a small amount of white sediment could be seen in the bottom of the tube. The length of time from the formation of the clot until the contents of the tube became clear was recorded as

the clot lysis time. When lysis occurred in 48 hours or less, the sterility of the tube was verified by culturing its contents on a blood agar plate or on Brewer's anaerobic medium. If bacterial contamination was present, the test was not considered valid.

Since clot lysis frequently did not occur for many days, it was convenient to record the clot lysis time in days. A patient whose clot lysed in less than 24 hours was said to have a clot lysis time of one day; if the clot lysed between 24 and 48 hours, he was said to have a clot lysis time of 2 days, and so forth. Frequently, the clots were discarded after 10 days, and the clot lysis time then recorded as 10+ days.

EXPERIMENTAL

(1) *The Clot Lysis Time in Normal Human Beings.* The clot lysis times of 49 presumably normal human adults were determined in the manner described. The subjects included 33 men and 16 women, personnel or medical students at the Johns Hopkins Hospital, all of whom were apparently in good health. The blood was not drawn in any particular relation to meals or activity.

The clot lysis times of the normal adults have been recorded in Fig. 1A. In these normal human beings, the recalcified plasma clot, when incubated at 37°C., did not lyse in less than three days, and usually not for at least four days. The shape of the distribution curve for the clot lysis time of normal adults, however, suggests that occasionally a normal person's clot would lyse within one or two days. That this has not yet been observed may indicate that the sample is too small. However, under the conditions of this study, fibrinolysis was not observed in normal human adults in less than three days.

The clot lysis time of a number of subjects was determined repeatedly. In a small group of normal men, the clot lysis time did not usually vary more than a day or two from time to time. In women, on the other hand, considerable variation was noted from week to week. Thus, in one normal woman, the clot lysis time varied from 8 to 40 days, in another from 5 to 28+ days, and in a third from 4 to 24+ days. The significance of this variation in clot lysis time is not clear. In several young women fibrinolysis was more rapid at the time of menses than during the intermenstrual period. However, variation among subjects was great. Data on the relationship between fibrinolysis and the menstrual cycle will be reported separately.

(2) *The Clot Lysis Time in Patients without Evidence of Hepatic Disease.* The clot lysis times of 118 patients on the medical and surgical wards were determined in the manner described. These patients did not have hepatic damage that could be determined clinically or by the usual laboratory tests. The clot lysis times of these patients have been plotted in Fig. 1B. In the majority of patients without hepatic damage, the recalcified plasma clot did not dissolve before the third day of incubation at 37°C. Six of these patients had obstructive jaundice of short duration and without evidence of hepatic damage. Ascites due to tuberculous peritonitis was present in two patients.

In eight patients, however, the clot lysis time was two days or less. These patients did not have clear evidence of hepatic damage, as detected by clinical criteria or partial laboratory studies. Seven of these eight patients were males, although 41 per cent of the 118 patients were females. Certain data pertinent to the state of hepatic function in these patients have been tabulated in Table I. One patient with hemophilia had a lysis time of two days on two occasions; the clot lysis times in two other hemophiliacs were 5 and 10+ days respectively. Two patients with severe rheumatoid arthritis had clot lysis times of two days. One of these patients had evidence of hepatic damage. In the other, the clot lysis time three days after the first determination was 10+ days. In a third patient with rheumatoid arthritis, the clot lysis time was six days.

Three patients with rapid lysis times apparently were undergoing some form of intravascular hemolysis. One of these patients had sickle cell disease, another had polycythemia vera with jaundice, and a third had typhoid fever with hemoglobinuria and methemalbuminemia. The latter two patients had evidence of hepatic damage as well. However, in a patient with congenital hemolytic jaundice, another with sickle cell anemia, and a third with acquired hemolytic jaundice of unknown etiology, the clot lysis times were within the normal range. The clot lysis time was rapid in a patient with carcinoma of the esophagus, in another with multiple thromboses, in one with orthostatic hypotension, and a fourth with hypertensive cardiovascular disease.

In one patient with subacute bacterial endocarditis due to *Streptococcus mitis*, the clot lysis time was 6 hours, six hours after embolectomy and while the patient was being treated with dicumarol. Five days

TABLE I*

Rapid Lysis Time in Patients Without Hepatic Disease

PT.	AGE	SEX	DIAGNOSIS	LYSIS TIME	CF	TT	BILI.	I.I.	BSP	ALB.	GLOB.	ALK. PH'ASE	P.T.	UROBILIN-OGEN	BILIURIA
E. W.	75	M	Chr. alcoholism; carcinoma of esophagus	2 (11–19–46)				5		3.9	2.9				
R. M.	23	M	Hemophilia	5 (12–11–46) 2 (2–14–47) 2 (3–15–47)			2.3/1.3	10					>50%	1:10	
P. W.	23	M	Subacute bacterial endocarditis 6 hrs. post-op.; on dicumarol	1 (3–16–47) 10+ (3–21–47) 15+ (6–24–47)	Neg. Neg.	6.2 1.6	1.8/0.8			2.9	2.2		<25%		
J. N.	25	M	Sickle cell crisis	1 (3–22–47)	Neg.	4.9	7.9	50		4.0	2.7	14.3	>65%	1:80	
A. G.	35	M	Rheumatoid arthritis	1 (3–25–47) 10+ (3–28–47) 5 (9–17–47)	++	3.8	0.8	75		4.4	2.9	4.0			
H. C.	47	M	Orthostatic hypotension	1 (8–4–47)	Neg.	3.5	<0.8	5		4.6	1.7	5.5			
E. R.	46	F	Hypertensive cardiovascular disease	2 (2–17–47) 2 (2–19–47)	Neg.	9.6							>65%		
S. W.	64	M	Cerebral accident; multiple thromboses	2 (4–1–47)			<0.8								

* The laboratory studies recorded in this and the following tables were performed in the laboratories of the Chemical, Biological, and Clinical Microscopy Divisions of the Department of Medicine of the Johns Hopkins Hospital. The cephalin flocculation test (C.F.) is recorded as neg. to ++++. The thymol turbidity test (T.T.) is reported in arbitrary units (14); in this laboratory, the upper limit of normal is believed to be six units. Bilirubin values (Bili.) are recorded in mg. per 100 cc. of serum; where a fraction is reported, the larger value is total bilirubin and the smaller, direct-reacting bilirubin. Icterus Index (I.I.) is recorded in Meulengracht units; the upper limit of normal is 10. Bromsulfalein retention (BSP) is recorded in mg. of dye retained per 100 cc. of serum 30 minutes after intravenous injection of 5 mg. per kilo; the upper limit of normal is believed to be 1.0 mg. per 100 cc. of serum. Albumin (Alb.) and globulin (Glob.) values are in grams per 100 cc. of serum. The alkaline phosphatase (alk. ph'ase) values are recorded in Bodansky units. Prothrombin time (P.T.) is recorded as percentage of prothrombin compared with a normal plasma using an accurate standardized rabbit brain thromboplastin solution; the lower limit of normal is 65%. Urobilinogen is recorded as the greatest dilution of urine to give a positive test by the Wallace-Diamond method. Biliuria was detected by the foam test.

later and again six months later the clot lysis time was 10+ days. Five other patients under treatment with dicumarol had clot lysis times of three or more days. Macfarlane (3) reported that rapid fibrinolysis,

TABLE II

Laennec's Cirrhosis

NAME	AGE	SEX	LYSIS TIME	C.F.	T.T.	BILI.	I.I.	B.S.P.	ALB.	GLOB.	ALK. PH'ASE	P.T.	URO-BILIN-OGEN	BILIURIA	COMMENTS
J. V.	46	M	1 (11-7-46) 1 (6-20-47)	++ +++	17.4 13.1	3.0 1.8/0.8	9	4.9 4.5	2.6 3.3	3.9 4.5	6.4 6.1	45% >50%			Died; no autopsy
W. E.	44	M	1 (12-2-46)	Neg.	5.3	3.5/1.8		5.0	2.7	4.1	4.7	40%	1:80	Neg.	Died; no autopsy
F. S.	41	M	1 (4-14-47)	++++	9.3	35.0/20.2	75		2.3	3.4	10.3	30%	1:40		Died; autopsy
E. K.	40	M	2 (11-21-46)	Neg.	21.3	2.2/1.1		2.6	4.9	3.5					Confirmed at operation
J. K.	60	M	2 (12-16-46)	+	5.6	2.5/1.6	10		4.0	3.3	15.9	>65%	1:80		Died; autopsy; carcinoma of liver and cirrhosis
J. H.	56	M	2 (1-31-47)	++	8.8	7.5/4.8	70	4.1	2.8	4.2	7.2	30%	1:80	ft. trace	
C. F.	36	M	2 (2-14-47)	++	8.2		15	2.9	3.3	4.0	4.6	>65%	1:2		
V. M.	57	F	2 (3-1-47) 4 (6-6-47)	Neg. Neg.	9.4 9.6	<0.8 <0.8	10 6	2.2	3.1 4.4	1.7 2.5	3.0 4.7	>65% >80%			Improved, but died 10-18-47 of hematemesis; autopsy
R. M.	40	M	1 (2-17-47)	+++	17.8	7.9/4.4	20	5.2	2.7	3.6	11.0	35%	1:80		Died; autopsy
B. P.	60	M	2 (5-17-47) 3 (6-7-47)	+ Neg.	11.0 5.8	2.3/1.4 1.5/<0.8		2.8	3.4	3.2	8.2	100%	1:80		Improved
E. W.	65	F	1 (6-13-47)	++++	32.0	4.7/2.7			1.8	3.8	2.1	40%	1:50	Neg.	Died; no autopsy
M. H.	55	F	2 (6-19-47) 2 (10-3-47)	+++ +++	17.3 15.2	5.2/2.5 2.7/1.2	30 15	5.8 4.4	2.1 3.1	4.1 3.8	6.6 5.8	40% 50%	1:80	2+	Improved

M. H.	55	F	2 (6–19–47) 2 (10–3–47)	+++ +++	17.3 15.2	5.2/2.5 2.7/1.2	30 15	5.8 4.4	2.1 3.1	4.1 3.8	6.6 5.8	40% 50%	1:80	2+	Improved
L. W.	48	M	2 (6–20–47)	+	10.4	16.4/10.0		10.4	2.9	3.8	25.6	>50%	1:80		Died; autopsy: carcinoma of liver and cirrhosis
A. D.	44	F	1 (7–16–47) 1 (11–11–47)	++++ ++++	22.6 28.5	15.9/10.8 2.3/1.1	75 25	3.4 3.2	2.3 3.4	4.4 4.2	7.8 7.0	45% 35%	Neg. Neg.	4+	Improved
W. V.	61	M	1 (9–14–47)	++++	14.4	3.2/1.6	15	3.9	2.1	3.7	3.4	25%	1:80		Died; no autopsy
A. M.	43	F	11 (7–8–47)	Neg.	6.1	<0.8	9	1.5	5.4	2.4	14.3	>65%	1:40		Biopsy of liver; Paget's disease of bone
A. L.	51	M	3 (7–8–47)	+++	11.8	1.4/0.8	10		4.3	2.5	3.1	65%	1:80		
M. To.	58	M	1 (10–3–47)	++++	11.5	2.3/1.4	16	2.8	3.0	3.3	6.7	50%			
E. C.	33	M	1 (10–14–47) 4 (1–2–48)	++++	22.0	2.5/1.5	20	3.9	2.3	4.0	7.0	50%	1:20		Improved
B. F.	61	M	1 (10–10–47)	+++	13.6	3.0/1.4		2.6	2.3	3.7	6.7	50%			Died; autopsy
M. Ty.	63	M	2 (10–15–47)	++++	30.1	1.8/0.8		2.5	1.8	4.0		30%			Died; no autopsy
J. T.	57	M	2 (10–15–47)	+++	6.1	2.2/1.0	10	4.7	2.9	3.7	14.1	50%	1:80	Neg.	
S. H.	58	F	2 (11–3–47)	+++	7.8	<0.8	5	2.0	1.6	2.5	16.2	>50%			
J. J.	58	M	2 (11–14–47)	Neg.	15.5		7	4.2	3.4	3.6	7.0				Died; no autopsy
H. B.	44	M	2 (12–1–47)	Neg.	10.6	18.8/11.8	100		3.6	2.7	4.7	>50%	Neg.		
M. S.	75	F	1 (12–1–47)	++++	12.9	5.0/1.5	7.0	7.3	2.2	2.9	11.6	30%	1:10		Died; autopsy
R. G.	51	F	5 (10–21–47)	Neg.	7.7	<0.8	4	0.4	4.3	2.6	3.7	>80%	0	Neg.	Enlarged liver and esoph. varices
G. B.	35	M	2 (4–1–47)	Neg.	7.0	1.8/1.1	7.5	2.9	3.3	2.1	3.6	45%	1:80		
R. M.	39	M	2 (1–5–48)	++++	16.2	10.4/6.8	70		2.0	3.4	6.3	35%	1:256	4+	

measured by a different technique, was common postoperatively. However, in six other patients studied from 4 to 48 hours postoperatively, the clot lysis time was 4 to 25 days, values comparable to those observed in normal individuals.

In summary, then, the clot lysis time of hospital patients without overt evidence of impaired hepatic function was usually the same as that of presumably normal adults. In an occasional patient, however, rapid fibrinolysis did occur. The significance of this observation is not clear, but it is of note that in several of these patients active hemolysis was taking place at the time that the blood was drawn.

(3) *The Clot Lysis Time in Patients with Hepatic Disease.* The clot lysis times of 29 patients in whom the diagnosis of Laennec's cirrhosis was made on clinical or pathologic evidence are recorded in Fig. 1C, and the clinical data relative to the hepatic status of these patients, in Table II. Rapid fibrinolysis was an almost constant concomitant of cirrhosis of the liver. It will be recalled that rapid fibrinolysis was first described clinically in atrophic cirrhosis of the liver. On the other hand, in 13 patients with acute hepatitis due to various causes, the clot lysis time was always within normal limits. In only five of these patients was the test performed during the first week of the disease. However, two of these patients were in coma at the time the test was performed (Table III).

In 24 patients, evidence was present of impaired hepatic function during the course of some other disease. The data on these patients are assembled in Fig. 1D and Table IV. In 12 of these patients the clot lysis time was one or two days, and in all but three of the remaining patients, three days. Later, tests on several of these patients with rapid clot lysis times were normal. Two of the patients with rapid clot lysis times had undulant fever with hepatomegaly, and two had hyperthyroidism with evidence of transiently impaired hepatic physiology. In three other patients with hyperthyroidism, but without hepatic damage, the clot lysis time was normal.

In six patients with Laennec's cirrhosis, it was possible to follow the clot lysis time as the patient improved clinically. In two of these patients, whose disease was clinically milder than the others, the clot lysis time lengthened during the period of observation. In the other four patients, however, clinical improvement was not accompanied by any change in the clot lysis time.

TABLE III
Acute Hepatitis

TABLE III
Acute Hepatitis

PT.	AGE	SEX	LYSIS TIME	C.F.	T.T.	BILI.	I.I.	B.S.P.	ALB.	GLOB.	ALK. PH'ASE	P.T.	URO-BILIN-OGEN	BILIURIA	COMMENTS
S. S.	17	F	3 (1–31–47)	++	18.6	5.2/3.1	25	2.2			11.3		Neg.		Approx. 25th day
O. K.	29	M	4 (3–20–47)	+++	31.7	95.2/52.4	100		4.0	3.3	5.9	30%	Pos.	Pos.	8th day
H. B.	21	F	10+ (4–1–47)	+++	18.6		6	1.1							Approx. 60th day
E. J.	22	F	3 (4–4–47)	Neg.	10.4	4.1	15		4.9	3.2	3.0	>80%			5th week
G. F.	41	M	8 (6–9–47)	+++	19.2	20.0/12.9	100		3.6	3.1	9.0	>50%	1:320		10th day; comatose (?homol. ser. jaundice)
L. B.	39	F	7 (6–19–47)	+	3.2	6.2	50		3.5	1.9	7.7	>50%			5th day; toxic hepatitis due to ingestion of methyl alcohol and paint remover
L. L.	34	F	4 (10–9–47)	+++	32	6.4/4.4	50		4.1	4.0	5.9	100%	1:80		4th week; homol. ser. jaundice
M. G.	23	F	3 (10–9–47)	++++	31.7	7.0/4.9	75		3.6	3.9	16.0	40%	1:80	Pos.	19th day; 3rd recurrence
J. L.	24	M	4 (10–9–47)	+	4.0	10.4/7.1	50				7.5	>50%	1:20	2+	7th day
R. B.	4	M	15 (11–9–47)	Neg.	7.4	7.8/5.3			3.6	2.5	8.3	50%	1:10		7th day; comatose
E. R.	62	F	4 (11–11–47)	+++	17.8	13.2/9.4	50				10.7				2nd day (? homol. serum jaundice)
P. H.	24	M	3 (2–11–47)	Neg.	6.4	4.3/2.8	7.5		4.6	1.9	10.0		trace	Neg.	1st day
D. E.	25	M	10 (2–26–48)	++++	16.3	6.3/4.9	50	6.2	5.7	2.4	9.0	>50%	1:40		6th day

TABLE IV
Other Hepatic Pathology

PT.	AGE	SEX	DIAGNOSIS	LYSIS TIME	C.F.	T.T.	BILI.	I.I.	B.S.P.	ALB.	GLOB.	ALK. PH'ASE	P.T.	URO-BILIN-OGEN	BILI-URIA
W. S.	49	M	Hemochromatosis (biopsy)	7 (7–30–47)	Neg.	8.5	1.3/0.8		0.2	4.7	2.9	5.4	>80%	1:10	
R. L.	39	M	Wilson's disease with hepatosplenomegaly; autopsy	4 (12–3–47)			1.2/1.0			3.9	1.9	4.1			
D. J.	44	M	Undulant fever with hepatic insufficiency	3 (10–10–46) 2 (11–8–46)	+ Neg.	5.1 8.3	<0.8 <0.8		3.1 3.2	3.1 4.2	3.4 3.1	4.1 5.5		1:20	
T. P.	46	M	Undulant fever with hepatomegaly	4 (7–30–47) 2 (9–3–47) 6 (9–14–47)	 +++ ++++	 25.1 31.0	<0.8		0.5	3.2 4.3	2.9 3.8	3.4 4.7	>65%		
L. H.	31	M	Sickle cell anemia with hepatomegaly	3 (8–1–47)	++	17.6	10.8/5.7		19	3.9	3.2				
L. M.	43	F	Acquired hemolytic jaundice with hepatomegaly	5 (2–14–47)	++	11	3.9	15	2.8	4.3	3.4	2.5	>50%	1:40	
J. C.	56	M	Hypertensive C.V. disease with congestive failure and C.P.C. of liver	3 (11–7–46) 2 (11–11–46)	+ +	5.4 8.3	2.8/1.6	5		3.4	2.9	3.5	>80%		
K. S.	57	F	Hypertensive C.V. disease and C.P.C. of liver	3 (11–19–46)	Neg.	8.3	1.8/1.1		3.5	4.0	2.3	4.6			
T. J.	34	F	Rh. heart disease; C.P.C. of liver	3 (6–19–47)	Neg.	16.0	2.0		3.4	4.0	4.6				
L. W.	46	F	Hypertensive C.V. disease with C.P.C. of liver	3 (6–10–47)	Neg.	8.6	<0.8		2.5	3.8	4.3	4.4			
E. A.	43	F	Hyperthyroidism and pellagra	1 (2–11–47) 3 (2–19–47)	Neg. Neg.	6.2 4.9	2.3/1.1 <0.8		1.2	2.6 2.1	2.2 2.3	9.0 9.0			
H. C.	61	M	Hyperthyroidism	1 (9–3–47) 4 (9–7–47)	Neg.	3.2	1.2/1.1 <0.8	10 5	2.4	4.2	3.7	10.0 7.3		1:80	
A. K.	40	M	Carcinoma of stomach with	3 (11–15–46)	Neg.	10.9	15.8/10.5			4.0	2.9	15.7	>50%		

E. A.	43	F	Hyperthyroidism and pellagra	1 (2–11–47) 3 (2–19–47)	Neg. Neg.	6.2 4.9	2.3/1.1 <0.8			1.2	2.6 2.1	2.2 2.3	9.0 9.0				
H. C.	61	M	Hyperthyroidism	1 (9–3–47) 4 (9–7–47)	Neg.	3.2	1.2/1.1 <0.8	10 5	2.4		4.2	3.7	10.0 7.3		1:80		
A. K.	40	M	Carcinoma of stomach with metastases to liver	3 (11–15–46)	Neg.	10.9	15.8/10.5				4.0	2.9	15.7	>50%			
C. P.	76	M	Carcinoma of stomach; ascites and jaundice with ? metastases to liver	2 (3–15–47)	Neg.	1.6	25.8/17.2	75			2.6	2.8	15.9	<20%	1:10		
A. J.	52	F	Carcinoma, primary site unknown, with metastases to liver and bone	2 (6–10–47)	Neg.	5.1	<0.8						20.1	>50%			
B. G.	38	F	Carcinoma, primary site unknown with metastases to liver and lymph nodes	3 (10–23–47)	Neg.	19.2	2.0/0.8	10	6.2		2.8	3.8	31.5	40%	1:80		
H. R.	59	F	Diabetes mellitus; nodular liver at operation	2 (11–17–46)	Neg.	17.9	0.8		0.3		4.7	2.7		>80%			
T. M.	5 mos.	M	Biliary cirrh. & congenital absence of bile ducts (biopsy)	1 (3–22–47)	+++	1.8	57.0	11.6			3.9	3.3	20.3				+++
Z. W.	55	M	Pneumococcal pneumonia; chronic alcoholism & hepatomegaly	3 (4–19–47)	++	17.6	<0.8		0.4		3.3	5.0	4.1	>50%			
A. B.	40	M	Chronic alcoholism; hepatomegaly	3 (2–26–48)	Neg.	4.2	1.4/0.8	20					5.7	>65%	1:40		
G. L.	59	M	Chronic alcoholism; hepatomegaly	3 (1–12–48)	Neg.	12.8	1.4/0.8	10	2.7		5.1	3.4	3.8	>80%	Neg.		Neg.
A. W.	65	M	Rheumatoid arthritis with hepatomegaly	2 (10–10–47)	++	14.1	1.4/0.8		0.5		3.8	2.8	7.1	>65%	Neg.		Neg.
J. L.	25	M	Typhoid fever with hepatomegaly; hemolysis and methemalbuminemia	2 (11–6–47)	Neg.	11.2	2.2/1.0		3.0		3.5	2.7	4.0				
G. B.	59	M	Polycythemia vera and hepatomegaly	2 (3–19–47)	Neg.	4.0	5.4/2.7				4.3	2.3	2.3	>80%	Neg.		

Rapid fibrinolysis, then, was an almost invariable accompaniment of Laennec's cirrhosis of the liver. It was present also in patients who had hepatic damage during the course of some other illness, but was not observed either in acute hepatitis or in obstructive jaundice without hepatic damage.

DISCUSSION

The data presented indicate that in normal adults the recalcified plasma clot dissolved only after 3 or more days when it was incubated at 37°C. Moreover, the great majority of hospital patients had clot lysis times of three days or longer. On the other hand, in patients with chronic hepatic disease, particularly Laennec's cirrhosis, the plasma clot usually dissolved within two days, a phenomenon which could be demonstrated repeatedly.

The relationship between hepatic damage and rapid fibrinolysis was first noted by Nolf. He observed that rapid fibrinolysis occurred when Witte peptone was injected into hepatectomized dogs (4). If the liver was only temporarily excluded from the general circulation, restoration of the circulation of the liver would abolish the fibrinolytic effect of Witte peptone (5). If a dog was poisoned with phosphorus, an hepatic toxin, its blood became incoagulable, but when fibrogen was added, a clot occasionally formed which then dissolved rapidly (6). These studies suggest that rapid fibrinolysis might follow hepatic damage. In 1914, Goodpasture (1) showed that this was the case, for the clotted blood of patients with atrophic cirrhosis of the liver dissolved rapidly. This phenomenon never achieved wide popularity as a diagnostic measure, although the data presented suggest that it might be useful in determining whether hepatic damage is present in patients with ascites. It will be remembered that in the present study, two patients with tuberculous peritonitis without evidence of hepatic damage had normal clot lysis times.

Although the clot lysis time was rapid in patients with chronic hepatic disease, it was normal in each of 12 patients with acute hepatitis. This was even true in two patients in coma because of severe infectious hepatitis. One is led to speculate whether the phenomenon of rapid fibrinolysis does not indicate a fundamental difference in the pathologic physiology of acute and chronic hepatic disease, or whether it depends upon the duration of the illness.

Rapid fibrinolysis was also observed in eight patients in whom no evidence of hepatic damage was detected; i.e., about five percent of adults without evidence of hepatic damage had rapid clot lysis times. In so complex a phenomenon, this lack of correlation with hepatic damage in some patients is not surprising. Occasional reports of rapid fibrinolysis under a wide variety of conditions have appeared in the literature from time to time. Thus Macfarlane and his associates (3, 7) described rapid fibrinolysis in patients both pre- and postoperatively, and in patients with ulcerative colitis, rheumatic carditis, nephritis, serum sickness, Raynaud's phenomenon (with cold agglutinins), toxemia of pregnancy, lead poisoning, urticaria, and iritis. Other observers have reported rapid fibrinolysis in sudden death after intravenous mercurial poisoning (8), in toxemia of pregnancy and eclampsia (9, 10), and in normal individuals during menstruation (10), and after exercise or the injection of adrenalin (11). Rapid fibrinolysis has been reported on several occasions in patients with severe shock (12, 13). Thus Tagnon and his associates noted rapid fibrinolysis in 8 of 22 patients with medical shock; it is notable that two of these patients had cirrhosis of the liver with hemorrhage, presumably from esophageal varices. It should be emphasized that the technique for demonstrating fibrinolysis varied from study to study, so that comparisons are difficult.

Macfarlane pointed out that in many of the conditions under which he observed fibrinolysis the pathology has often been said to involve hypersensitive reactions. With this in mind, it is of interest that in three of the patients reported in the present study with one form or other of intravascular hemolysis the clot lysis was rapid. Whether an antigen-antibody reaction played any rôle is not clear.

Mechanisms controlling the rate of fibrinolysis have been discussed elsewhere (15). Briefly, plasma has long been known to possess proteolytic activity capable of digesting fibrin. However, the rate of fibrinolysis could not be related to the proteolytic activity present in plasma. Furthermore, plasma has been known to possess an agent which inhibits the plasma proteolytic enzyme. The rate of fibrinolysis could not be related to the activity of this inhibitory agent. However, the agent in fresh plasma which inhibited proteolytic enzyme was found to be unstable and its period of activity was variable. It was short-lived in the sera of patients whose clots lysed rapidly and long-

lived in those whose clots lysed more slowly. The speed of clot lysis, therefore, was dependent upon the stability of an antagonist in plasma to the proteolytic activity of the plasma.

SUMMARY

(1) The lysis time of recalcified plasma clots incubated at 37°C. was determined for 49 normal human adults and 184 patients on the wards of a general hospital.

(2) In all of these normal adults, and 93 percent of 118 patients without evidence of hepatic damage, the clot lysis time was three days or longer.

(3) In 26 of 29 patients with Laennec's cirrhosis, and in only seven percent of patients without evident liver disease, the clot lysis time was two days or less.

(4) In 13 patients with acute hepatitis and six with obstructive jaundice, the clot lysis time was three days or longer.

(5) In 24 patients with hepatic damage due to other causes, the clot lysis time was two days or less in 12, and three days in all but three of the remainder.

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SOME MANIFESTATIONS OF REFLEX ACTIVITY IN SPINAL MAN WITH PARTICULAR REFERENCE TO THE OCCURRENCE OF EXTENSOR SPASM

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Although the sequelae attending partial injuries of the spinal cord form a fairly common syndrome in civilian practice, the long-surviving patient with complete severance of the cord has been a rare clinical entity. However, the recent world conflict with its large number of casualties from high-velocity missiles resulted in a moderate number of such subjects. Application of the considerable medical and surgical advances of recent years, together with rapid, efficient evacuation, greatly increased the initial survival rates in these men. Paraplegia Centers established during the war employed new techniques of bladder management, assiduous hospital care, and careful medical and physical rehabilitation. These and other factors combined to increase markedly individual and group longevity as compared with the average life span of patients suffering similar injuries during World War I. Coincidentally, an opportunity was provided for the study of an unprecedented number of men with traumatic lesions of the spinal cord.

A brief preliminary report on the occurrence of extensor spasm in spinal man has been published by the authors (1). It is the purpose of this study to present detailed observations relating to certain involuntary activity patterns exhibited by long-surviving patients with complete severance of the spinal cord. Initial observations were made on these men during the summer of 1946, and subsequent studies were continued to March, 1948.[1] Each patient was subjected to neurological examination at frequent intervals. Marked changes in the reflex activities of different patients did not occur. The neurologic examina-

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[1] The data were completely indexed during the latter months of 1947, at which time the senior author was Chief of Surgery, Paraplegia Service, Cushing V A Hospital, Framingham, Mass.

tion detailed in each case history, therefore, is an examination selected as representative of the reflex activities manifested by that patient.

Heretofore it has been generally assumed that, after recovery from spinal shock, men with total transection of the cord exhibit only flexor spasms of the lower extremities, if they demonstrate any involuntary movements. This assumption appears to rest solely upon the observations of Head and Riddoch who, in 1917, conducted an intensive study of eight patients with verified anatomic cord transection and numerous other patients suffering from complete "physiologic" interruption of the cord or from partial cord lesions (2, 3). Repeated examinations of their transected patients indicated that progression from the stage of spinal shock to one of heightened reflex activity was characterized by certain highly specific findings. Their conclusions may be summarized as follows: On recovery from spinal shock, movements of the flexor type are the only primary motor reactions observed in cases of complete transection of the spinal cord. Diphasic movements of flexion and extension of the lower limbs resembling locomotion are never observed, and the extension following flexor contraction is due entirely to relaxation of the flexor muscles and to gravity. Extensor thrust is never seen. The tone of the flexor muscles is consistently higher than that of the extensors, and the knee and ankle jerks are mere twitches. In direct contrast to this group, those patients with "physiologic" (quotation marks ours) transection or with partial cord damage demonstrate primary extensor motor reactions; movements of locomotion and extensor thrust are present; the weak knee jerk is superimposed upon a tonic contraction of the quadriceps; and the penis and scrotum represent the areas of optimal excitability for evoking unilateral or bilateral extension of the lower limbs.

It has been inferred quite generally that, by study of the activity of the flexor and extensor reflexes of the lower extremities, it is possible to determine whether the cord has or has not been completely interrupted. In reference to movements of extension, Head and Riddoch stated:

> "The presence of this postural mode of response depends upon the integrity of certain descending propriospinal paths which link up the centres in the pons and medulla. Should these paths be grossly interfered with, primary extension is no longer possible, although the total damage to the spinal cord may be far from complete."

Since the publication of this classic study of spinal man, the principal criterion used in establishing a diagnosis of total severance of the cord has been the absence of extensor spasm in muscle groups below the level of transection. This criterion has been accepted as an all-or-none rule by many neurologists. Fulton (4, p. 136) maintains that

> "Instances of spinal paraplegia are seen with complete loss of sensibility below the level of the lesion, and yet they may have marked extensor spasm if the limbs are manipulated, especially if the leg is elevated from the popliteal space. *This is an unfailing sign of an incompletely divided cord* and may be of value both in diagnosis and prognosis."

Grinker (5, p. 388) similarly states:

> "Paraplegia-in-extension . . . is found in partial cord lesions. It is produced by trauma . . . and never when the cord is completely transected."

Russell Brain endorses the theory that extensor hypertonia depends upon the integrity of the vestibulospinal tracts and that destruction of the latter results in a dominant flexor reflex. He writes:

> "After a traumatic lesion, causing immediate and complete severence of the cord . . . paraplegia-in-extension never occurs, because the vestibulospinal tract is interrupted from the beginning, and as soon as the stage of spinal shock has passed, paraplegia-in-flexion develops." (6, pp. 603–604)

Bing and Haymaker (7, pp. 55–56) state:

> "If in transverse lesions of the spinal cord a flexor withdrawal reflex is present, one should determine whether or not, after withdrawal, the limb in question extends again. The presence of withdrawal only . . . signifies that the transection is complete. If after the withdrawal the extremity becomes extended . . . the transection is incomplete."

On the Paraplegia Service of the Cushing Veterans Administration Hospital, we have had the opportunity to study 27 verified cases of complete transection of the spinal cord in white males. The levels of transection ranged from D-2 to D-12. In every instance, transection had occurred two or more years prior to the period of examination. Two of these men showed only flexor spasm, two exhibited approximately equal flexor and extensor spasm, and eighteen showed predominant extensor spasm. In no patient was extensor spasm alone elicited.

Five men were completely flaccid and demonstrated no reflex activity in the musculature innervated below the level of cord section. At the time of writing, all of these men are alive, and most are in good general

TABLE 1

Type, degree, and duration of spasm in twenty-seven patients with complete severance of the spinal cord

	PATIENT	SEGMENTAL LEVEL OF TRANSECTION	TIME LAPSE SINCE INJURY*	DURATION OF SPASMS*	DOMINANT SPASM PATTERN
			days	*days*	
1	D. K.	D-2	889	847	Extension 4+, Flexion 2+
2	J. Z.	D-3	969	949	Extension 4+, Flexion 1+
3	V. H.	D-3	830	712	Extension 4+, Flexion 2+
4	R. S.	D-2	995	946	Extension 2+, Flexion (+)
5	A. S.	D-3	1,225	0	Completely flaccid
6	T. Mc.	D-4	1,075	985	Extension 4+, Flexion 1+
7	J. Dr.	D-3	1,040	958	Extension 4+, Flexion 1+
8	J. T.	D-4	1,098	0	Completely flaccid
9	R. B.	D-5	1,088	998	Extension 0, Flexion 2+
10	D. P.	D-5	986	866	Extension 3+, Flexion 1+
11	P. P.	D-5	971	940	Extension 4+, Flexion 1+
12	T. M.	D-5	736	0	Completely flaccid
13	M. D.	D-6	1,211	1,001	Extension 4+, Flexion 2+
14	J. B.	D-6	1,311	1,056	Extension 3+, Flexion 1+
15	P. C.	D-6	841	820	Extension 3+, Flexion (+)
16	R. P.	D-6	1,102	0	Completely flaccid
17	H. F.	D-7	851	830	Extension 0, Flexion 4+
18	G. G.	D-8	909	888	Extension 4+, Flexion (+)
19	J. D.	D-8	864	684	Extension 3+, Flexion 3+
20	J. W.	D-8	1,100	1,079	Extension 4+, Flexion 2+
21	J. V.	D-9	1,195	1,015	Extension 3+, Flexion 1+
22	L. D.	D-9	719	539	Extension 4+, Flexion 2+
23	D. L.	D-9	1,181	1,121	Extension 4+, Flexion (+)
24	F. B.	D-10	985	893	Extension 4+, Flexion 2+
25	W. M.	D-10	1,174	1,144	Extension 3+, Flexion 3+
26	E. G.	D-7	1,283	0	Completely flaccid
27	W. D.	D-12	953	773	Extension 3+, Flexion 1+

* Calculations to Oct. 1, 1947.

(+) = Flexion movements minimally present.

physical condition. The extreme reflex activity manifested by many patients in this series has been permanently abolished by anterior dorsolumbar rhizotomy.

The results of our observations are summarized in Table 1. In each of the following case reports, the sources of the data in the first two paragraphs were the patient and his clinical records, respectively, except for the surgical procedures carried out personally by one of us.

Case 1, D. K., age 36, sustained multiple rifle bullet wounds on April 24, 1945, with immediate loss of sensation and voluntary movement below the level of the nipples. X-rays demonstrated severe comminution of the laminae of D-2. Exploratory laminectomy one month later revealed a gap of 1 cm. in the spinal cord at the level of the second dorsal vertebra.

The first involuntary movements appeared approximately six weeks after injury and consisted of "toe-wiggling." Spasms of the abdomen, back and both lower extremities began a few weeks later and flexor spasm reached its maximal severity within four months after injury. Activity then gradually became primarily extensor in type. The upright position proved to be the most effective stimulus for the production of extensor spasms. No autonomic manifestations associated with changes in skeletal muscle tonus were observed. Erections have been infrequent, usually incomplete, and there has been no evidence of ejaculation.

Neurologic examination, 27 months after transection of the cord, revealed a predominant extensor spasm pattern in the skeletal musculature below the level of the lesion. Generalized extension of the lower extremities was invariably evoked by shifting the patient from a sitting to a supine position. The maneuver produced a response which involved the skeletal musculature below the costal margins in rigid extension that was maintained for three to four seconds. The rigidity[2] was followed by a stage of relaxation occupying one to two seconds. Intermittent squeezing of the thighs elicited prolonged extension of both lower extremities. Light touch applied to either thigh produced extension to a lesser degree. The clasp-knife phenomenon was easily demonstrated. Manipulation of the skin of the abdomen, gluteal and lumbar regions provoked no movements. Rubbing of the scrotal skin evoked mild extensor spasms, but never complete rigidity. Penile manipulation elicited poorly sustained turgor of the shaft, with no discernible muscle movements.

Nociceptive stimulation of the plantar areas resulted in hallux dorsi-flexion, spreading of the toes, and classic triple-flexion of the lower extremities. No crossed responses were noted. Midline perineal stimulation resulted in bilateral triple-flexion.

The deep abdominal reflexes could be elicited in all quadrants. The cremasteric reflexes were absent bilaterally. Knee jerks were 4+ bilaterally with sustained patellar clonus, and the latter was frequently masked by rigid extension of one or

[2] Here, and elsewhere in this report, the term "rigidity" denotes a skeletal muscle response similar to the "rigid pillar" phenomenon which characterizes the positive supporting reaction.

both extremities. The ankle jerks were 3+ bilaterally with poorly sustained clonus. Dilatation of the rectal sphincter resulted in no discernible responses. The Babinski responses were strongly positive.

Case 2, J. Z., age 22, sustained multiple machine-gun wounds on February 3, 1945. He became immediately paralyzed from the level of the nipples downward. X-rays disclosed compound, comminuted fractures of the second and third dorsal vertebrae, and evidence of fragmentation of the neural canal at that level. Exploratory laminectomy on December 4, 1946 revealed a complete anatomic severance of the spinal cord with a gap between the ends.

Involuntary movements of the lower extremities were first noted twenty days after injury when "someone pulled the hairs along my right thigh and the leg jumped." Bilateral flexor spasms gradually manifested themselves and within six months had become quite frequent and vigorous. It became necessary to tie the patient to his bed as a safety measure. Occasional extension spasm occurred, but it was not until 18 months after injury that the strength and frequency of extension became marked. Stepping movements were noted and sudden overall rigidity would stiffen him out on the bed or slide him out of his wheel-chair. Erections were present since date of injury, but there were no ejaculations.

Neurologic examinations two years and two months after injury disclosed that, although extension spasm was not precipitated by plantar stimuli, it became manifest immediately if the thighs were stroked or squeezed, if pressure was applied at the popliteal region, or if the patient was shifted from a sitting to a supine position. Rigidity was generalized from the level of the xiphoid distally and sustained approximately five seconds. If one lower extremity was elevated by lifting at the popliteal space, initial ipsilateral extension occurred and frequently, after a definite lag, crossed to the opposite extremity. Rapid lowering of the straight lower extremity evoked severe ipsilateral extensor stiffening which invariably crossed and resulted in generalized extension. Rigidity of the adductor musculature was a prominent feature of this picture.

Noxious stimuli to plantar areas elicited dorsiflexion of the four toes with no movements of the hallux, moderate dorsiflexion of the foot, and sharp tugging flexion at the knee and pelvis. Crossed phenomena included plantar flexion of the foot and visible tightening of the anterior and posterior thigh musculature. The abdominal wall was not involved in the flexion reflex. The right lower extremity failed to demonstrate complete triple-flexion, but was considerably stronger in extensor manifestations than was the left.

The superficial abdominal reflexes were absent; the deep ones were 2+ in all quadrants. The knee jerk was 4+ on the right with sustained patellar clonus and 3+ on the left with frequent masking by extensor rigidity. Ankle jerks were 2+ bilaterally with sustained clonus. The sign of Babinski was not elicited.

Case 3, V. H., age 22, was struck by a bullet on June 20, 1945, and experienced immediate sensory and motor paralysis below the level of the nipples. X-rays demonstrated irregularities of the 4th and 5th dorsal vertebrae. An exploratory

laminectomy performed in May, 1947, revealed complete transection of the cord at D-3 with an extensive gap between the rostral and distal stumps.

Involuntary quivering movements of the feet and toes were first noted approximately four months after injury, whenever the soles were lightly touched. Gradually the knees began to twitch, and flexion at knee and hip became noticeable. Ten months after their appearance, spasms had reached their maximum, and exhibited no change during the ensuing months. "Stiffening-out"[3] movements occurred soon after the first extensor movements were noted, and flexion alternated with extension after spasms became severe, though extension has been consistently predominant. Bicycling movements were noted frequently. Spasms have been severe enough during the past year to necessitate lashing the lower extremities to the bed each evening. On maneuvering between bed and wheelchair, the patient was commonly troubled by extension severe enough to cause extreme rigidity of the trunk and lower extremities. Erections began simultaneously with flexor manifestations, were complete, and evoked by any type of penile manipulation. Ejaculation has never occurred.

Frequent neurologic examinations 25 months after injury demonstrated essentially similar spasm patterns. Movements of extension were consistently more marked than those of flexion. The former were evoked by almost any type of manipulation excepting nociceptive stimuli to the plantar or genital zones. They were characteristically precipitated by a change from a sitting to a supine position. Such a stimulus resulted in smooth, powerful extension, converting the trunk and lower extremities into a "rigid pillar." Light stroke along the thigh evoked strong ipsilateral extension, but crossed extensor movements were infrequent. The more rostral the area of stimulation the greater was the tendency for crossed phenomena. Light stroking of the perineum and scrotum initiated bilateral extension. Manipulation of the penile shaft evoked slow and incomplete erection, but no other evidence of activity unless the thighs or scrotum were inadvertently contacted. Any attempt to lift either lower extremity, especially if the force was applied at the popliteal space, resulted in immediate generalized extensor rigidity of the limb with crossed increase in extensor tone and, occasionally, bilateral rigidity.

Nociceptive stimulation of the plantar surfaces resulted in hallux dorsiflexion, spreading of the toes, and triple-flexion of the lower extremities. Midline pinprick of the perineum and external genitalia resulted in bilateral triple flexion, the response being unilateral with slight deviation of the stimulus to either side.

Deep abdominal reflexes were present in all quadrants. Knee jerks were 4+ bilaterally with no patellar clonus. Ankle jerks were 3+ bilaterally with poorly sustained clonus. Cremasteric responses were absent bilaterally. The sign of Babinski could be demonstrated in each lower extremity.

Case 4, R. S., age 22, was injured by a bullet on January 8, 1945. He sustained an immediate paralysis below the level of the nipples. X-rays revealed a com-

[3] Words of the patient.

pound fracture of the body and laminae of the second dorsal vertebra. Laminectomy the day after injury disclosed a completely pulped and liquefied cord at the level of the second dorsal vertebra. The liquefied matter was removed, leaving a gap of several cms. between the rostral and caudal cord.

Involuntary movements of the toes were first noted five weeks after injury. Within three months, flexor spasms had spread to hips, thighs, and legs. With drawal activity was so constant and severe a month later that surgical relief was advised but the patient refused. Triple-flexion was frequently bilateral at this stage. After one to two months at peak activity, spasms began to decrease in strength and "sensitivity" and, coincidentally, extensor movements appeared and slowly increased in severity. Seven months after injury, flexion had definitely become a minor part of the spasm picture, and extension remained dominant to the present date. The patient has been able to stand without braces or other support for periods as long as one minute before buckling occurs at the hips or knees. He has noted that the act of reclining supine is especially productive of bilateral trunk and lower extremity extension spasms. Erections have been frequent since injury and easily elicitable by manipulation. Ejaculation has been noted on two occasions, accompanied in each instance by extremely severe extensor rigidity.

Neurologic examination 2 years and 8 months after injury revealed a weak, incomplete flexion reflex. The extension pattern was considerably stronger and more easily elicited. Primary extension could be precipitated by lowering the patient from a sitting to a supine position and was manifested by rapid tightening of the trunk, pelvic and lower extremity musculature. Rigidity was not well maintained, however, and relaxation occurred within a few seconds. Rapid lowering of the elevated extremity to the bed resulted in generalized quivering extension of the ipsilateral limb, but crossing was rare, and quite incomplete, when it did occur. Rubbing or squeezing the skin of the thighs elicited no responses. The adductor muscles exhibited moderate hypertonus in the resting state and passive separation of the thighs served to increase adductor tone markedly. Percussion of one adductor tendon resulted consistently in bilateral adductor contraction, drawing the thighs strongly together. Erection occurred readily with gentle penile manipulation, but there was no ejaculation, and no muscle movements.

Nociceptive plantar stimulation provoked weak flexor muscle contractions but did not result in movement of the extremity. There was moderate hallux dorsiflexion, fanning of the remaining toes, dorsiflexion of the foot and visible contraction of the thigh musculature. Noxious stimuli applied to the genital area did not elicit muscle responses.

The superficial abdominal reflexes were 2+ in the upper and absent in the lower quadrants. The deep abdominals were 2+ in all quadrants. The cremasteric reflexes were not elicited. The knee jerks were 4+ with unsustained clonus bilaterally. The ankle jerks were 3+ with unsustained clonus.

Case 5, A. S., age 27, sustained multiple machine-gun wounds on May 23, 1944. He experienced immediate sensory and motor paralysis below the level of the

nipples. X-rays demonstrated comminuted fractures of the 3rd and 4th dorsal vertebrae. Exploratory laminectomy within 48 hours of injury disclosed a completely severed spinal cord at the level of D-3.

The patient has never noted muscle movements in any paralyzed part of his body.

Neurologic examinations three years and five months after injury revealed a completely flaccid paralysis below the level of the D-3 dermatome. No perceptible muscle response occurred to a variety of stimuli. Deep and superficial reflexes were not elicited. The anal sphincter was patulous.

Case 6, T. McC., age 32, was struck in the chest by a shell fragment on October 20, 1944. There was immediate and complete loss of sensation and motor power below the level of the nipples. X-rays revealed comminuted fractures of the laminae of D-5 and D-6 with fractures of the vertebral ends of the right fifth and sixth ribs. Exploratory laminectomy on February 14, 1947, disclosed a complete absence of spinal cord substance at the vertebral levels of D-3, D-4, and D-5.

Three months after cord transection, while his feet were being washed, the patient noted quivering movements of the toes. Gradually, involuntary withdrawal spasms appeared in the lower extremities. Six months post-injury, examination revealed flexor spasms rated as 2+, bilateral unsustained patellar clonus, and complete lack of response of the feet or toes to plantar stimulation. Extension spasm became manifest at this time and slowly increased in severity. Two years after cord transection, stepping and bicycling movements had become quite violent and it was necessary to tie the patient to his bed or wheelchair. Primary extensor rigidity was made especially severe by weight-bearing in the upright position, and brace ambulation was impossible. Erections were directly associated with spastic activity, occurring more frequently as spasms increased in severity. There were no ejaculations.

Neurologic examinations two years and five months after cord transection revealed a patient with remarkably strong and varied involuntary movements. At times, activity appeared to be spontaneous. Reflex activity was self-propagated for periods of many minutes. The dominant spasm pattern was extension. Plantar stimulation elicited bilateral extensor rigidity, unusual in that the stiffened lower extremities lifted slightly at the hips and traveled slowly from side to side like a horizontal pendulum, the arc gradually decreasing to the midline. The tightly apposed extremities then slowly dropped to the bed, where "plastic" relaxation eventually occurred. With more intense plantar stroke, the bilateral rigidity was followed almost immediately by a smooth, rapid abduction of the stimulated limb, the latter lifting and swinging outward from its taut hinge at the pelvis. After a definite lag, the contralateral extremity followed, maintaining close approximation to its fellow. Return to the midline was followed by eventual relaxation. Mild plantar pinprick produced similar extensor phenomena and repeated stimuli occasionally established synchronous stepping or bicycling movements. Almost any non-noxious contact with the extremity, such as stroking,

squeezing and occasionally merely touch, evoked complex extensor responses. Extensor thrust was powerful and sustained, and the clasp-knife phenomenon easily demonstrated in either lower extremity. Shifting from a sitting to a supine position invariably precipitated extension so severe as to "knock out the breath" of the patient during the period that rigidity was sustained. Erections were easily evoked by penile manipulation, but no muscle activity occurred. There was no ejaculation.

Strong pinprick of the plantar and genital areas resulted in quick, jerking withdrawal of the ipsilateral limb, but there were no movements of the hallux or toes. Relaxation was occasionally abrupt, but more frequently the triple-flexed extremity waved uncertainly in the air, rotating at the hip for many seconds before sinking slowly on the bed, where extensor rigidity supervened. Midline perineal pinprick produced bilateral lower extremity withdrawal, without movements of the feet. Noxious stimuli to abdomen, thighs or legs evoked no significant responses.

The superficial abdominal reflexes were absent, the deep were 1+ bilaterally; knee jerks were 4+ bilaterally with severe patellar clonus, masked rapidly by extensor rigidity. Ankle jerks were 4+ and clonus was checked by extensor spasm. No toe movements were elicited.

Case 7, J. D., age 34, was struck by shell fragments on November 24, 1944. He immediately lost all sensation and motor power below the level of the nipples. X-rays disclosed fractures of the 3rd and 4th dorsal vertebrae. Laminectomy on November 14, 1947, revealed a complete transection of the spinal cord at the level of D-3.

Two weeks after injury, bilaterally positive Babinski signs were noted. One month later, withdrawal reflexes were obtained by stroking the inner aspects of the thighs. The patient was first cognizant of reflex activity four months after injury when weak flexion movements of the knees occurred. This involuntary activity gradually spread to hips, back and abdomen. Approximately nine months after injury, the left lower extremity began to exhibit extension. At the end of one year, extensor spasms had become completely dominant in both lower extremities, although the right lower extremity still occasionally exhibited flexor spasms. He noted stepping movements frequently, but no bicycling. Extension has frequently "thrown him" from his wheel-chair by lifting his hips forward and stiffening out the trunk and both lower extremities. Erections have been frequent since injury and occur with any non-noxious penile stimuli. There have been no ejaculations.

Neurologic examinations two years and 10 months after injury revealed extremely strong and active extensor spasms, easily provoked by shifting the patient from a sitting to a supine position or by squeezing the anterior thigh musculature. Primary extension occurred immediately, converting the trunk and lower extremities into a rigid framework; the belly hard, hips and knees locked, thighs tightly apposed, and feet pointed in extreme plantar flexion. Rigidity persisted for approximately five seconds and relaxation was smooth and simultaneous in all spastic muscle groups. Pressure beneath the popliteal space did not usually cause extension, but as passive flexion began at the hips there was immediate powerful

resistance; gradual melting of this resistance was accompanied by steady tightening of the ipsilateral hamstrings and adductors, drawing the leg up and adducting the thigh. Passive hyperflexion resulted in sudden relaxation of the thigh musculature and the clasp-knife phenomenon was thus demonstrable. Forceful flexion of the thigh with the leg fully flexed provoked strong extensor thrust at the hip, which ceased immediately with release of pressure. Although extension could be elicited in one lower extremity alone, crossing was frequent and spread of extension was dependent upon the intensity of stimulation. Penile manipulation evoked complete erection within 30 seconds, without muscle movements of trunk or extremities. There was no ejaculation.

Nociceptive stimulation of the plantar areas elicited strong hallux and foot dorsiflexion, followed by the movements of classic triple-flexion.

The superficial abdominal responses were present in all but the left upper quadrant; the deep reflexes were 1+ bilaterally. The knee jerk on the left was 2+ and on the right 3+. All attempts to elicit clonus resulted in primary extension of the limb being manipulated. The ankle jerk was 3+ on the left and 2+ on the right, with no clonus elicitable. The sign of Babinski was present bilaterally.

Case 8, J. T., age 29, was injured on September 27, 1944, by a shell fragment, and experienced complete sensory and motor paralysis below the level of the nipples. X-rays revealed comminuted fractures of the 5th and 6th dorsal vertebrae. Exploratory laminectomy on December 3, 1946, revealed a 3 cm. gap between the ends of the spinal cord at the level of injury.

Since the date of injury the patient has noted no movements in the paralyzed part of his body.

Neurological examinations three years after injury revealed a completely flaccid paralysis below the level of the D-5 dermatome. Various maneuvers and stimuli failed to elicit muscle movements of any type. The superficial and deep reflexes were absent below the level of transection, and the anal sphincter was patulous.

Case 9, R. B., age 28, was struck in the chest and spine by a bullet on October 7, 1944. There was immediate sensory and motor paralysis below the level of the nipples. No bony fractures occurred. A second exploratory laminectomy on September 25, 1945 revealed a completely crushed cord at the level of D-5 and apparent conduction of sensation through many fine fibers associated with the dura. The dura and scarred proximal and distal ends of the cord were completely excised, leaving a considerable gap in the spinal cord. There is no indication that this procedure changed the neurologic status of the patient.

Involuntary movements in the abdominal muscles were noted approximately three months following injury. Gradually these weak twitchings increased in severity and spread to the back and lower extremities. Withdrawal spasms were intense within five months of injury and it became necessary to tie him to his bed each evening. Involuntary movements were flexor in type with moderate adduction, and at no time did he note extension. Two weeks following spinal cord excision in September of 1945, weak bilateral lower extremity flexion began and within a month. withdrawal spasms reached their old intensity. The abdominal involve-

ment seemed to have decreased in severity, but flexion manifestations were unchanged. There was no stepping or bicycling, but he discovered that stimulation of one sole often caused flexion of the contralateral limb. Despite bilateral obturator nerve section and adductor tenotomy, thigh adduction and scissoring was a frquent occurrence. Withdrawal movements were common even while sitting in a wheelchair. Erections were easily elicited with any non-noxious penile stimulation, but ejaculation was not noted.

Neurologic examinations three years after spinal cord injury revealed severe generalized atrophy of the hips and lower extremities, and chronic flexion contractures of approximately 25° at both knees. Extensor muscle masses were practically non-existent, while the hamstrings were palpable as small, firm bands. The right lower extremity demonstrated more activity to a given stimulus than the left. No movements of the hallux were observed with plantar stimulation, but there was moderate dorsiflexion of the remaining toes, strong dorsiflexion of the foot and definite jerking contraction of the thigh flexors. There were no crossed movements even with severe plantar stimulation. On the left, toe movements were absent, but the other responses, though attenuated, were similar to those elicited on the right. Rubbing of the scrotal skin elicited bilateral hamstring contraction, and pinprick at the genital area provoked ipsilateral or bilateral triple-flexion, dependent upon whether the stimulus was midline or to one side. Erections occurred rapidly with penile manipulation and were complete. There was no ejaculation and no muscle movements attended penile stimulation.

The superficial abdominal reflexes were absent, the deep 2+ in each quadrant; the right knee jerk was 2+, the left 1+. No patellar clonus was elicited. Ankle jerks were absent bilaterally. The sign of Babinski was not present.

Case 10, D. P., age 25, was struck in the upper spine by a bullet on January 17, 1945, and rendered immediately and completely paralyzed from the nipple line downward. X-rays demonstrated a fracture of the laminae and left pedicle of the 5th dorsal vertebra and a bullet partially imbedded in the body of that vertebra. Exploratory laminectomy on August 9, 1946, revealed that the missile had pierced the spinal cord, severing it. Removal of the foreign body left a wide gap between the stumps of the spinal cord.

Approximately four months after injury, jerking movements of the knees were noted. The patient appreciated the fact that his soles were "sensitive," and weak withdrawal movements were experienced. Within three months, bilateral flexion spasms became severe, and nine months after transection, extreme scissoring activity was ameliorated by bilateral obturator and tibial nerve neurotomies. Crossed flexor movements were noted at this period. Sixteen months after injury, triple-flexion began to alternate with brief episodes of extension and bicycling occurred frequently. Gradually, extensor spasms increased in severity and, two years after severance of the cord, were more frequent and powerful than flexion spasms. The most provocative stimulus for extension was a shift from a sitting to a supine position, though the patient noted that the spasms were evoked also by weight-bearing on the soles. The rigidity proved to be of considerable assistance in maintaining

the upright position. During expecially active periods, vigorous shaking of the rigid lower extremities occurred, usually terminated by forcible passive flexion of the leg at the knee. Erections were frequent and sustained, but there were no ejaculations.

Neurologic examinations two years and six months after complete severance of the spinal cord demonstrated a moderate extension spasm pattern and weak withdrawal responses in the lower extremities. Extension could be precipitated by squeezing the muscles of either thigh or by having the patient recline supine on his bed. The extensor rigidity thus provoked was sustained only for three to four seconds before relaxation occurred. Crossed reflexes were demonstrated only by postural change or by vigorous manipulation of the limb, and the musculature below the xiphoid participated generally in the rigidity so produced. There was mild resistance to upward pressure at the popliteal fossa, but the limb easily became movable and freely mobile at all joints. The clasp-knife phenomenon was rather poorly demonstrated. Lateral and medial rotation of the relaxed extremity usually evoked ipsilateral extension, but no crossed muscle responses. Manipulation of the msucles and skin of the abdomen, hips, and legs elicited no muscle contractions whatsoever. There was no extensor thrust. The patient could evoke rather prolonged and rigid extension by "arching" his back repeatedly. Erections were easily produced by penile manipulation. There were no ejaculations.

The deep abdominal reflexes were 1+ in all quadrants. Knee jerks were 3+ with unsustained clonus, occasionally masked by primary extension of the stimulated limb. Ankle jerks were 2+ bilaterally and clonus was not elicited. The Babinski reflex was strongly positive in each lower extremity.

Case 11, P. P., age 21, received multiple machine-gun wounds on February 1, 1945, and was immediately and completely paralyzed below the level of the nipples. X-rays disclosed a compound, comminuted fracture of the 5th dorsal vertebra. Exploratory laminectomy, on February 2, 1945, revealed a compressed but intact cord at that vertebral level. On January 29, 1947, prior to an anterior rhizotomy, re-exploration revealed a large syringomyelitic caivity in the cord at D-5. The sac was excised, leaving two slightly scarred stumps with a 2 cm. gap between them. There was no evidence that this procedure in any way altered reflex activity.

The first movements noted in the paralyzed extremities began approximately one month after injury and consisted of slight flexion spasms at the knees. These gradually increased in severity and a moderately strong withdrawal pattern was present seven months post-injury. A tie-sheet became necessary during the night. Adduction spasms were producing marked scissoring at this time. Ten months after injury, extension spasms appeared and gradually assumed dominance over the involuntary flexion movements. Triple-flexion occurred infrequently one year after injury, but as the extensor movements decreased slightly during succeeding months, flexor spasms reappeared and stepping and bicycling were often noted. Erections were easily elicited with almost any non-noxious stimulation of the penis. No ejaculations were noted.

Neurologic examinations two years after injury and one month after excision of

the syringomyelitic sac disclosed a predominant extensor spasm pattern. Extensor rigidity of the trunk and lower extremities was easily elicited by shifting the patient from a sitting to a supine position, by gently rubbing the thigh or by squeezing the thigh musculature near the knee. Allowing the flexed, relaxed limb to slide flat of its own weight produced ipsilateral extension that frequently crossed in the trunk musculature, but infrequently involved the contralateral extremity. Definite resistance to flexion was encountered at both the hip and knee when pressure was applied at the popliteal space, and after forced flexion the clasp-knife phenomenon could be demonstrated in either limb. Rubbing of the skin of the skin of the legs, abdomen, or lumbar areas evoked no movements. Erections were rapidly evoked by penile manipulation and were unaccompanied by muscle movements. There was no ejaculation.

Jerking flexor movements were elicited by noxious stimuli to the plantar areas. Dorsiflexion of the hallux and four toes was followed in rapid succession by foot dorsiflexion, contraction of the thigh flexors and spasm of the ipsilateral lumbar musculature. Crossed phenomena included plantar flexion of the foot and fleeting primary extension of that extremity. Midline penile or perineal stimuli elicited bilateral withdrawal spasms of both lower extremities.

The superficial abdominal reflexes were absent, the deep ones 3+ bilaterally. The cremasteric responses were active. Knee jerks were 4+ bilaterally with sustained clonus unless masked by extensor rigidity. The ankle jerks were 2+ with bilaterally unsustained clonus. The sign of Babinski was strongly positive bilaterally.

Case 12, T. M., age 24, was struck in the spine by a shell fragment on September 24, 1944. He experienced immediate sensory and motor paralysis below the mid-chest. X-rays revealed comminuted fractures of the 7th, 8th, and 9th dorsal vertebrae. Exploratory laminectomy on December 22, 1944, disclosed a complete transection of the cord at the D-7, D-8 vertebral level, with considerable fibrosis and atrophy of the visible caudal cord.

Since date of injury the patient has noted no muscle movements below the level of his lesion.

Neurologic examinations three years after injury disclosed a completely flaccid paralysis below the level of the D-8 dermatome. Various stimuli and maneuvers failed to elicit muscle movements in the paralyzed portion of his body. Superficial and deep reflexes were absent, and the anal sphincter was completely atonic.

Case 13, M. D., age 26, was injured on June 7, 1944, by multiple shell fragments. He immediately lost all sensation and motor power below the mid-chest. X-rays revealed gross fractures of the 6th and 7th dorsal vertebrae. Exploratory laminectomy on July 19, 1946, revealed a complete transection of the spinal cord at the level of the 6th thoracic vertebra.

Week "jerking" movements at the knees were noted approximately seven months after cord transection. They slowly increased in severity until both lower extremities demonstrated moderate withdrawal responses. One year after injury, extensor spasms appeared and gradually became stronger and more frequent.

Bilateral sustained ankle clonus was observed in October, 1945. Stepping occurred frequently, but there were no sustained periods of bicycling. Spasms did not necessitate lashing him to the bed, but occasionally extension was of sufficient strength to lift him bodily from his wheel-chair. The erect position strongly stimulated trunk and lower extremity extension and he was then unable to flex at the hips. Frequency of erections was directly related to increased spasm. No ejaculations were noted.

Neurologic examinations three years and four months after injury revealed a dominant extension spasm pattern, provoked especially by the act of reclining from a sitting position. Rubbing the anterior surfaces of the knees or lower thighs produced similar responses, the entire body below the xiphoid transforming into a "rigid pillar." The stiffened lower extremities frequently jerked clonically as they lifted slightly at the hips, the severe thigh adduction obliterating all inter-thigh space and the feet and toes strongly plantar flexed. Rigidity thus provoked was maintained five to six seconds, and was followed by smooth, plastic relaxation over a somewhat shorter interval. Straight-leg raising evoked immediate strong resistance at the hips and, when this was overcome, the clasp-knife phenomenon was demonstrable. Rubbing either popliteal region elicited rapid bilateral extension, maintained for the usual period. Unilateral extension was infrequent, for the abdominal and lumbar responses were invariably bilateral. Involvement of the contralateral lower extremity seemed to be directly related to the strength of the stimulus. Erections were easily evoked by manipulation, although no ejaculation occurred. No muscle movements accompanied penile manipulation.

Nociceptive stimuli on the left sole elicited a strong hallux dorsiflexion with the usual abrupt jerking flexor contractions at leg, thigh and pelvis. On the right, all toes demonstrated quivering plantar flexion. No crossing was noted during such stimulation, nor was the abdominal musculature involved in this reflex pattern. Midline perineal pinprick frequently resulted in bilateral withdrawal movements.

Stroke across the left lower abdominal quadrant consistently evoked contractions in the right upper quadrant. Deep abdominal reflexes were 2+ in all quadrants. Knee jerks were 4+ bilaterally. On the left, clonus was masked by extensor rigidity; on the right, clonus was unsustained. Ankle jerks were 4+ bilaterally, with bilateral sustained clonus. The Babinski response was marked on the left, absent on the right.

Case 14, J. B., age 23, sustained a compression fracture of the 6th and 7th dorsal vertebrae as a result of a parachute jump on February 25, 1944. He developed immediate sensory and motor paralysis from the mid-chest down. Surgery was deferred until December 1944 when a laminectomy revealed a complete transection of the cord at D-6.

Eight and one-half months following injury the patient noted twitching of both knees. Involuntary movements increased from mild flexion spasms to severe classic triple-flexion, and the right lower extremity was noted to be consistently more active than the left. By mid-1945 extensor spasms began to appear, straightening him out rigidly on the bed. There was no bicycling. One year after injury

spasms were so severe that it was necessary to lash the patient to his bed each evening. On a number of occasions extensor rigidity lifted him bodily out of his wheel-chair. Frequency and severity of spasms began to decrease by January, 1946, and reached the present level of activity two years and three months following cord transection. Moderate flexor and extensor spasms are now manifested, and the latter are consistently more severe. Erections have been frequent since date of injury and occur readily with any type of non-nociceptive manipulation of the penis. Ejaculations have not been noted.

Neurologic examinations two and one-half years after injury revealed a dominant extensor spasm pattern. Complete extension was easily produced by shifting the patient from a sitting to a supine position. Generalized rigidity occurred, involving the body from xiphoid to toes, the abdomen becoming board-like, while the pelvis and distal joints locked. When the palm was placed beneath either knee joint and gentle lifting pressure exerted, bilateral primary extension was a frequent result. The knee and hip strongly resisted flexion, but with persistent pressure the clasp-knife phenomenon could be eventually demonstrated. Squeezing of the anterior thigh consistently produced ipsilateral extension and frequently, generalized bilateral extension. Light brushing contact along the posterior thigh evoked the same phenomena. Strong adductor contraction was always an accompaniment of extension.

Nociceptive stimulation at the sole or genital areas evoked triple-flexion movements which were consistently stronger on the left. There was no movement of either hallux during this or other stimulation. Crossed phenomena were never observed to accompany withdrawal responses.

The deep abdominal reflexes were 2+ in each quadrant and the cremasteric reflex strong on the left, but less marked on the right. Knee jerks were 4+ bilaterally. There was sustained clonus on the left, and clonus was masked by extensor rigidity on the right. Ankle jerks were absent bilaterally. The sign of Babinski could not be elicited.

Case 15, P. C., age 23, was struck by shell fragments on January 11, 1945. He immediately lost all sensation and voluntary motor power below the rib cage. X-rays revealed a comminuted fracture of the 6th dorsal vertebra. Laminectomy eight hours after injury disclosed a completely crushed and liquefied cord at that level, with no anatomic continuity between the proximal and distal stumps.

Spasms began approximately three weeks after injury with quivering movements of the toes. A typical withdrawal pattern gradually developed. Neurologic examination two months after laminectomy disclosed 3+ knee jerks, with a Babinski sign and ankle clonus on the right. Mild extension soon was noted, and within two and one-half years of injury, powerful extensor spasm had developed. Violent shaking of the rigidly extended lower extremities occurred frequently. Bicycling was not noted. During succeeding months the vigor and frequency of all involuntary movement gradually decreased, but extensor components retained their relative dominance. Erections have been frequent and easily evocable by manipulation, but ejaculation has not occurred.

Neurologic examinations two years and nine months after injury revealed a patient whose involuntary movements had subsided to the extent that they were not easily elicited by ordinary stimuli. However, both extensor and flexor patterns could be elicited and the predominant muscle contractions were of an extensor type. If the patient elevated his hips by pushing upward beneath his buttocks, primary extension occurred, locking the trunk and lower extremities in rigid extension. Manipulation of the lower extremities could be carried out without perceptible resistance, but straight leg-raising provoked ipsilateral hamstring tightening. The adductors were moderately taut bilaterally and brisk external rotation of the thigh provoked a rigid, trembling ipsilateral extension that was maintained for 2–3 seconds, and then quickly relaxed. Squeezing or rubbing of the thighs elicited no responses. In the standing position the lumbar, pelvic and thigh musculature exhibited marked increase in tone. The erect position was maintained without braces and with only the balancing support of the hands. Any non-noxious contact with the penile shaft elicited rapid, complete erection, and the latter was sustained with stimulation. No ejaculations occurred, and there was no extraneous muscle movement noted during such stimulation.

Nociceptive stimuli to the plantar areas resulted in dorsiflexion of the ipsilateral hallux and foot, and abortive triple-flexion. Crossed movements did not occur.

The superficial abdominal reflexes were absent; the deep abdominal reflexes were 2+. A fleeting left cremasteric response was noted. Knee jerks were 4+ bilaterally with sustained clonus and ankle jerks were 3+ bilaterally with unsustained clonus. The Babinski response was marked bilaterally.

Case 16, R. P., age 26, was injured by machine-gun fire on September 13, 1944. He experienced immediate sensory and motor paralysis below the mid-chest. X-rays revealed a cominuted fracture of the body and laminae of the 6th dorsal vertebra. Exploratory laminectomy the day after injury disclosed a complete severance of the cord at the level of the D-6 vertebra, with a sizable gap between the ends.

The patient has not noted movements of the musculature innervated below the level of the lesion since time of injury.

Neurologic examinations three years after cord transection revealed a completely flaccid paralysis below the level of the D-6 dermatome. Severe nociceptive stimuli failed to elicit any perceptible responses. Superficial and deep reflexes were absent, and the rectal sphincter atonic.

Case 17, H. F., age 23, was injured on June 1, 1945, by shell fragments which produced an immediate sensory and motor paralysis from the level of the 7th rib downward. X-rays revealed metallic foreign bodies within the spinal canal at the 7th and 8th dorsal vertebrae. Exploratory laminectomy on August 29, 1946, revealed a 4 cm. scar surrounding a large fragment of metal within the spinal canal at the level of the 7th dorsal vertebra. There was a large gap in the spinal cord following removal of both scar and fragment. This procedure produced no apparent change in the neurologic status of the patient.

Twitching movements began in the hips approximately three weeks after cord

injury and gradually spread to the lower extremities. Withdrawal was consistently stronger on the left. Occasional severe adductor spasms occurred. Increase in the frequency and severity of the involuntary movements continued for 16 months, during which time the patient noted occasional "stiffening-out" spasms, but they occurred only under very special circumstances. Flexion deformities of the lower extremities appeared and it was necessary to tie the patient to his bed whenever he occupied it. Erections were first noted four months after injury and recurred frequently as a result of light contact or irritating stimuli to the penis. There were no ejaculations.

Neurologic examinations two years after cord transection disclosed severe symmetrical atrophy of the hips and both lower extremities. The right lower extremity was drawn up in a permanent flexion contracture of 15 degrees at the knee, and there was little substance to the extensor muscle groups bilaterally. Extensor movements could not be elicited. Plantar stroke or pinprick resulted in strong hallux dorsiflexion with marked fanning of the remaining toes, dorsiflexion of the foot, flexion of the leg on the thigh, and flexion with strong adduction of the thigh. The abdominal and lumbar musculature stiffened bilaterally. No other crossed responses were detected. Lowering the patient from a sitting to a supine position precipitated bilateral withdrawal reflexes. Noxious stimuli applied to calves, thighs, or abdomen either elicited no response or, rarely, triple-flexion of one or both lower extremities. Midline penile or perineal pinprick provoked bilateral withdrawal. Erections were easily evoked by penile manipulation, but ejaculation did not occur and no muscle movements were noted.

Superficial abdominal reflexes were absent. The deep abdominals were 2+ bilaterally; knee jerks were 2+ with no clonus. Ankle jerks were 2+ bilaterally and clonus was absent. Strongly positive Babinski signs were present bilaterally.

Case 18, G. G., age 24, was struck by shell fragments on April 24, 1945, sustaining fractures of the right pedicle and both laminae of the 8th dorsal vertebra. He experienced immediate sensory and motor paralysis below the level of the rib cage. Laminectomy on April 9 revealed a lacerated dura beneath the laminae of D-8 and a 0.5 inch gap in the spinal cord at the level.

Involuntary movements were noted three weeks after injury when toe and foot twitching appeared on the right side. Spasm gradually spread to involve the flexor muscles and the patient developed bilateral withdrawal responses. Extensor movements began after triple-flexion had become well marked. Gradually extensor spasms assumed dominance. Sudden extensor rigidity would then frequently lift him bodily from his wheelchair, stiffening him out from xiphoid to toes. Scissoring spasms of the thighs occurred frequently in the sitting position.

Neurologic examinations two years and five months after transection of the cord revealed a strong and persistent extensor activity. Almost any maneuver caused immediate generalized extension. If the flexed lower extremity was held by the heel and gently extended passively, a powerful driving thrust developed and the limb stiffened into extension, its partner extending almost as rapidly. Ipsilateral extensor movements could be effectively evoked by the light stroke of a finger

along the thigh. Crossed movements were extremely common and the clasp-knife phenomenon consistently demonstrable. Pressure, and occasionally touch, at the popliteal fossa produced primary extension, making it virtually impossible to lift the extremity until the musculature had been given ample time to relax. Maintenance of generalized extension resulted in gradual penile engorgement, and erection was complete within 30 seconds. Erection could be easily evoked by manipulation, in which case no muscle movements occurred. There was no ejaculation.

Nociceptive stimuli applied to the plantar areas resulted in the muscle contractions characteristic of classic triple-flexion, but these were neither forceful nor sustained, and the stimulated limb often did not lift from its relaxed position.

The superficial abdominal reflexes were absent; the deep ones were present and 2+ bilaterally. The cremasteric reflexes were present and vigorous, but elicitable only from a sharply circumscribed area the size of a silver dollar at the medial aspect of each mid-thigh. Knee jerks were 4+ bilaterally with sustained clonus.

Case 19, J. D., age 25, was injured by machine-gun fire on June 18, 1945. He sustained immediate sensory and motor paralysis below the waist, and X-rays disclosed a bullet within the spinal canal at the level of the 8th dorsal vertebra. An exploratory laminectomy on March 26, 1947, disclosed an anatomically complete transection of the cord with a gap between the ends.

Weak twitching movements at the knees were first noted approximately six weeks after injury. Typical withdrawal spasms gradually manifested themselves, but at three months post-injury, the lower extremities would occasionally straighten out rigidly. He developed alternating flexion and extension spasms, but extension did not become powerful nor did flexion continue to increase in severity. From day to day, either flexion or extension might predominate, and he believed the movements to be of equal intensity. Erections were noted within a few days after injury and priapism has occurred intermittently since, with no evidence of ejaculations.

Neurologic examinations two years after injury revealed approximately equal flexor and extensor manifestations. The right lower extremity exhibited stronger triple-flexion than the left. Extension was provoked by straightening the partially flexed extremity; by shifting the patient from a sitting to a supine position; or by gentle pressure beneath the knee. Primary extension was thus produced, crossed movements being manifested predominantly in the trunk musculature, but also in a consistent contralateral tightening of the adductor muscles. Clonic jerking of the entire limb was succeeded either by abrupt triple-flexion or by extensor rigidity. Bilateral extension was not noted. If one extremity was held in full flexion and the sole of the contralateral extremity stimulated, a complete reversal of pattern occurred, the flexion of the limb stimulated occurring simultaneously with crossed extension. The clasp-knife phenomenon was evokable bilaterally. Penile manipulation led to partial erection. There was no ejaculation. No muscle movements attended penile stimulation.

Withdrawal response to minimal plantar stimuli was vigorous and immediate. Strong hallux dorsiflexion and fanning of the remaining toes was rapidly succeeded

by dorsiflexion of the foot and strong contraction of the ipsilateral hamstrings, adductors, and iliopsoas. If the opposite extremity was in a position of passive flexion at the knee, this reaction-pattern crossed, but if extended, the crossed extension was greatly augmented. Severe nociceptive stimuli to the genital areas only occasionally evoked flexor movements and these were incompletely manifested.

The superficial abdominal reflexes were absent; the deep reflexes were 2+ in all quadrants. Knee jerks were 3+ bilaterally and patellar clonus was frequently masked by extensor rigidity. No cremasteric responses were elicited. The ankle jerks were 3+ bilaterally with sustained clonus. The Babinski response was bilaterally positive.

Case 20, J. W., age 27, was wounded by shell fragments on September 25, 1944. He sustained immediate and complete paralysis below the waist. X-rays demonstrated comminution of the laminae and pedicles of the 9th dorsal vertebra. Laminectomy October 15, 1946, at the site of a previous unsatisfactory exploration revealed a transected cord with a 1 cm. gap between the stumps.

Twitching of the low back muscles was noted approximately three weeks after injury. As the involuntary movements became stronger, activity spread to the anterior abdomen and thence down both lower extremities. A strong withdrawal pattern developed and within seven months of injury, his lower extremities were so active that it was necessary to lash him to his bed in order to prevent falls. Bilateral jack-knifing was quite common, and the right lower extremity consistently exhibited more activity than the left. One year after injury, he was beginning to note extensor spasm and with succeeding months, extension occurred more and more commonly. Flexor spasms simultaneously decreased in vigor and the patient noted that lifting himself from the bed to the wheelchair often precipitated rigid extension. Pelvic extension was a material aid in helping him maintain an erect posture. Flexor activity while sitting in the wheelchair was noted occasionally. Apparently spontaneous erections were complete while the patient still retained a urethral catheter. After its removal they were partial and ejaculations were never noted.

Neurologic examinations two years and four months after injury disclosed a dominant extension spasm pattern. The threshold for production of such activity was sufficiently low so that plantar stroke evoked ipsilateral lower extremity extension with crossed hallux plantar flexion. If the flexed extremity was allowed to slide flat on the bed, primary ipsilateral extension occurred and crossing was quite rapid, resulting in generalized stiffening of the paretic trunk and lower extremtieis. The extremity originally stimulated exhibited hallux dorsiflexion, while the contralateral hallux was invariably plantar flexed. Lifting beneath the knee consistently evoked ipsilateral extension with crossing and the same overall picture. The clasp-knife phenomenon was well demonstrated bilaterally. Squeezing of the thighs provoked moderate extension that frequently crossed after a definite lag. Partial erection was produced with penile manipulation and was unattended by muscle movements. There was no ejaculation.

Nociceptive stimuli on the plantar surface elicited the movements of triple-

flexion, but much less completely and vigorously than similar stimulation at the upper inner thigh and genital areas. The only crossed response was plantar flexion of the hallux. Flexor spasm was bilateral, when evoked by stimuli at the perineal midline.

The superficial abdominal reflexes were absent in the upper and 2+ in both lower quadrants. The deep abdominals were 3+ in all quadrants. The knee jerks were 4+ bilaterally and clonus was rapidly masked by extension. The ankle jerks were 4+ with bilateral sustained clonus. The sign of Babinski was bilaterally strongly positive.

Case 21, J. V., age 26, was injured on June 23, 1944, by shell fragments which fractured the right pedicle of the D-9 vertebra and fragmented D-11. There was immediate sensory and motor paralysis from the mid-abdomen down. Laminectomy performed on June 30, 1944, revealed a complete transection of the cord with a gap between the ends at the level of the tenth dorsal vertebra.

"Bucking" movements of the pelvis while the patient was in a prone position were noted six months after injury. One year later, when the patient began to ambulate, he noted jerking at the knees, together with strong dorsiflexion of the feet. A moderate withdrawal pattern developed bilaterally. Extensor movements occurred at this time and flexion and extension movements began to alternate. There was frequent "stepping" but never well-propagated bicycling, and the right lower extremity was always more active than the left. Gradually the extensor pattern became dominant and the flexor spasms simultaneously decreased in vigor and frequency. The patient frequently was able to stand without braces, supported by the strong extension which occurred with weight-bearing on the plantar surfaces. Erections were frequent, and were provoked by any non-noxious moving contact with the penis. There was no evidence of ejaculation. The patient has been married the past six months and states that he is capable of maintaining intercourse indefinitely when he so desires.

Neurologic examinations three years and three months after injury disclosed a predominant extensor spasm pattern. Squeezing the muscle masses of either thigh, or lifting the extremity at the popliteal space, evoked primary extension of the ipsilateral limb, and frequently crossed extension. Shifting of the patient from a stitting to a supine position provoked bilateral extensor rigidity without involvement of the abdominal musculature. Strong adductor contraction was part of the extensor pattern. Tapping the adductor tendon would consistently elicit bilateral adductor contraction. Gentle rubbing of the penis provoked rapid and complete erection, sustained as long as the stimulus was continued.

Flexor spasms were easily elicited by nociceptive stimulation of the plantar surfaces, and were characterized by bilateral strong hallux dorsiflexion and classic triple-flexion of moderate severity. These movements were more vigorous and prolonged in the left lower extremity. Elicitation of a withdrawal reflex resulted in contralateral adductor muscle contraction.

The superficial and deep upper abdominal reflexes were present and 2+; the lower abdominals were absent. The cremasteric reflex was not elicited. The

knee jerk was 4+ on the left; patellar clonus could be evoked but was rapidly succeeded by extensor spasm. The knee jerk was 3+ on the right with no clonus. The ankle jerk was 3+ on the right with mild unsustained clonus; 2+ on the left with no clonus. Bilateral Babinski responses were marked.

Case 22, L. D., age 30, was injured on December 21, 1945, when he fell 50 feet from a hangar roof. He sustained immediate, complete sensory and motor paralysis from the mid-waist down. X-rays demonstrated comminuted fractures of the 9th and 10th dorsal vertebrae. Exploratory laminectomy the day after injury disclosed considerable bony and soft tissue damage, and the spinal cord was found completely divided at D-9, D-10, with a gap between the ends.

Involuntary movements were first noted in the feet approximately six months after injury. The lumbar muscles became active and within a few months the patient exhibited bilateral triple-flexion responses. Extension spasms began at this time and slowly increased in severity. Within one year of injury, it became necessary to tie the patient to his bed each evening unless he slept on his side. This peak in the severity of involuntary activity was maintained approximately three months. The spastic manifestations then subsided to a moderate vigor and sensitivity. Bicycling movements were not experienced. Enforced bed rest increased spastic activity markedly. Though spasms frequently interfered with brace walking, the patient believed that the extension occurring with weight-bearing was a distinct postural advantage. Erections began about two months after the first involuntary movements occurred and were easily evoked by manipulation. Ejaculations were not noted.

Neurologic examinations two years after injury disclosed a dominant extensor spasm pattern. The most provocative stimulus for eliciting generalized extensor rigidity was a shift of the patient from a sitting to a supine position. Lowering of the elevated straight leg provoked strong ipsilateral extension that rapidly crossed to involve the contralateral rextremity. Squeezing or rotating the relaxed thigh elicited weaker extension responses, usually restricted to the ipsilateral trunk and lower extremity, dependent usually on the vigor with which stimulation was carried out. Bilateral extensor rigidity was frequently interrupted by rapid, clonic flexor movements at the hips, but these intermittent spasms were succeeded by complete rigidity and the latter was maintained 4–6 seconds before plastic relaxation occurred. Rubbing of the thigh surfaces evoked feeble responses or none at all. Lifting beneath the popliteal region infrequently excited ipsilateral extension. Forcible passive hip flexion of the straight lower extremities sometimes evoked weak contralateral extension, sometimes abortive crossed triple-flexor movements. Penile manipulation resulted in rapid erection, sustained with stimulation and unaccompanied by skeletal muscle activity. Ejaculation did not occur.

Nociceptive stimuli applied to the plantar areas resulted in triple-flexor movements of moderate activity. Hallux and foot dorsiflexion were quite marked in comparison to the remainder of the reflex picture. Pin stroke across the left lower abdominal quadrant evoked sharp contraction in the left upper quadrant. The deep abdominal reflexes were 2+ in all quadrants. Knee jerks were 3+ bilaterally

with unsustained clonus, frequently masked by extensor rigidity. The right ankle jerk was 3+, the left 2+ with bilaterally unsustained ankle clonus. Babinski responses were strongly positive bilaterally.

Case 23, D. LaR., age 24, was struck by shrapnel on July 6, 1944. There was immediate sensory and motor paralysis below the level of the rib-cage. X-rays revealed compound, comminuted fractures of the laminae of D-8, D-9, and D-10. Laminectomy on July 12, 1944 disclosed a necrotic and completely severed spinal cord at the level of the D-9 vertebra.

Involuntary twitching movements began in the abdomen and small of the back approximately two months after injury. Muscle activity spread quite rapidly and within a few months vigorous withdrawal reflexes were present. Six months after onset, flexion began to alternate with extension; stepping movements occurred for prolonged periods and the patient was frequently jerked out of bed by sudden severe spasms. Activity was maintained at this high level, although the pattern gradually changed from combined flexion and extension to bilateral extension with weak flexor movements, then reverted to flexion-extension once more. The back muscles were active and quite powerful during early post-injury days, but their activity gradually decreased. Priapism was frequent and could be elicited by manipulation. There was no ejaculation.

Neurologic examinations three years after injury disclosed a strongly dominant extensor pattern. The most effective stimulus for overall trunk and lower extremity rigidity was a shift of the patient from a sitting to a supine position. This commonly resulted in violent, rhythmic shaking of the extended lower extremities, followed by a period of rigidity lasting six to eight seconds. Pressure beneath the knee of either relaxed extremity provoked immediate ipsilateral extension and frequently caused crossed extensor spasm, depending upon the vigor of the maneuver. After extension was forcibly overcome, the clasp-knife phenomenon was consistently demonstrable. Hyper-flexion of the leg with the thigh acutely flexed evoked crossed extension, and forced extension of the leg with the thigh at the same angle elicited crossed triple-flexion. Squeezing of the thigh provoked ipsilateral extension with infrequent crossing. The left lower extremity was slightly more active in flexor and extensor movements than the right. Complete erection was easily produced by penile manipulation; no ejaculation occurred, and no muscle movements accompanied manipulation.

Nociceptive stimuli applied to the plantar areas elicited the jerking movements of classic triple-flexion on the side stimulated. There were no crossed movements. Midline penile and perineal pinprick evoked bilateral triple-flexion, with, however, no movement of feet or toes.

Stroke or pinprick of the left lower abdominal quadrant elicited vigorous contraction in the right upper quadrant. The deep abdominals were present and 2+ bilaterally. The knee jerks were 4+ bilaterally with unsustained clonus. The ankle jerks were 2+ bilaterally with weak, unsustained clonus. The Babinski sign was strongly positive bilaterally.

Case 24, F. B., age 34, was injured by shell fragments on January 19, 1945, and

sustained immediate, complete sensory and motor paralysis below the mid-waist. X-rays demonstrated a comminuted fracture of the 10th and 11th dorsal vertebrae. Exploratory laminectomy the day of injury revealed a complete transection of the spinal cord at the level of D-10.

The first involuntary movements of the lower extremities were noted approximately three months after cord transection and consisted of toe "jiggling." Gradually a withdrawal pattern of activity developed bilaterally, at first characterized by jerking movements of the knees, and "bucking" at the hips while lying prone. Six months after injury the triple-flexion pattern was moderately active, although it was not necessary to tie the patient to his bed during sleep. Sixteen months after transection, the reflex activity was interfering both with mat exercises and with attempts at ambulation. Extensor spasms began at this time and slowly increased in severity. He found it very difficult to passively flex his strongly extended lower extremities while dressing himself and occasionally extensor rigidity caused him to slide out of his wheel-chair. The act of reclining from a sitting position was invariably productive of extensor spasm. Bicycling and stepping were not noted. The right lower extremity was consistently more active in all reflex manifestations than the left. Erections were present since very early post-injury days, but ejaculation was not noted.

Neurologic examinations two years and four months after cord transection revealed strongly dominant extensor spasms. Primary extension was evoked by a number of maneuvers, including shift of the patient from a sitting to a supine position, upward pressure beneath the knee, and squeezing of the thigh musculature. Crossed movements were frequent, and moderate stimulation resulted in overall muscle rigidity from the mid-abdomen to the toes; the hips locked, the extremities tightly apposed, and feet and toes pointed. When the initial rigidity excited by leg-raising had subsided, the clasp-knife phenomenon was demonstrable at the knee bilaterally. Unilateral extension alone was occasionally elicited by gentle stroking of the skin of the thigh, but if activity was severe, crossed reflexes always occurred. Similar stimuli applied to the skin of the abdomen or legs rarely evoked spasm. Erections were easily produced by penile manipulation, but ejaculation did not occur.

Nociceptive stimulation of the plantar areas resulted in moderately vigorous withdrawal spasm with dorsiflexion of the hallux and foot, and flexion of the leg and thigh. All movements were abrupt in both contraction and relaxation phases. Crossed reflex movements were not noted. Midline perineal or penile pinprick caused bilateral triple-flexion.

The superficial abdominal reflexes were absent; the deep ones were present only in the lower quadrants. There were no cremasteric responses; the knee jerks were 4+ bilaterally, and frequently clonus was masked by extension. The ankle jerks were 3+ bilaterally and clonus was unsustained. The Babinski responses were bilaterally positive.

Case 25, W. M., age 23, was injured July 13, 1944, by a rifle bullet which severely traumatized the left upper arm and eventually lodged within the spinal canal at the

level of the tenth dorsal vertebra. It was necessary to amputate the left upper extremity about 6" below the shoulder. Laminectomy at the site of injury three days later disclosed a "contused" cord. Re-exploration on February 12, 1947, revealed a dense scar within the spinal canal at the level of the 10th dorsal vertebra. This scar was excised, leaving a 2 cm. gap between the proximal and distal stumps. Removal of the cicatrix had no apparent effect upon his neurologic status.

Involuntary movements began approximately one month after injury with twitching at the left knee. Shortly thereafter, flexion spasms of the thigh appeared and gradually the movements spread to both lower extremities. Spasms became so powerful that 18 months after injury it was necessary to lash the patient to the bed as a protective measure. Two years after injury, flexor spasms were maximal and it was at this time that extension movements began to appear. As the latter gradually increased in frequency and severity, the flexor pattern slowly subsided and withdrawal manifestations became less powerful. He no longer needed restraint while in bed, and was able to sleep on his abdomen with only occasional "bucking" movements at the hips. Bicycling occurred infrequently. Erections have been frequent, but there has been no ejaculation.

Neurologic examinations three years after injury, and after the scar excision, revealed both flexor and extensor patterns in the lower extremities. Each pattern was of moderate strength and quite easily evocable. The left lower extremity demonstrated sharper, stronger responses in all phases of triple flexion than did the right. Plantar stroke elicited violent dorsiflexion of the hallux and foot, followed by sharp, jerking flexion of leg on thigh and thigh on pelvis. Moderate extensor thrust was elicited, but release of pressure on the sole resulted in relaxation of the limb in the partially flexed position. Noxious plantar stimulation of the right lower extremity elicited only feeble triple flexion, immediately followed by ipsilateral extension and contralateral hallux dorsiflexion, the hallux slowly relaxing as rigidity melted from the stimulated limb. The clasp-knife phenomenon could easily be demonstrated on the right. Hyperflexion of the left leg on the thigh produced crossed extension much more frequently than was produced by a similar maneuver of the right leg. Nociceptive stimuli applied to the genital area provoked strong downward contraction of the ipsilateral lower abdominal muscles and a coincident ipsilateral triple-flexion. Midline pinprick of the perineum caused bilateral triple-flexion.

The superficial abdominal reflexes were absent; the deep ones were weak but present in all quadrants. The left knee jerk was 4+ with sustained clonus and the right 3+ with unsustained clonus. The left ankle jerk was 4+ and clonus was sustained. The right ankle jerk was 3+ with unsustained clonus. There was a well-marked Babinski response on the left. Penile manipulation resulted in rapid, complete erection, but ejaculation did not occur. No muscle movements accompanied non-noxious penile stimulation.

Case 26, E.G., age 32, was shot in the back on March 26, 1945. He experienced immediate complete sensory and motor paralysis below the level of the rib-cage. X-rays revealed comminuted fractures of the 5th and 6th dorsal vertebrae. Ex-

ploratory laminectomy on April 25, 1945 disclosed complete necrosis of the cord at the level of the D-7 vertebra. Aspiration of this material left a wide gap between the ends of the cord.

Since the date of injury the patient has noted no muscle movements in the paralyzed parts of his body.

Neurologic examinations two years and four months after injury revealed a completely flaccid paralysis in the musculature innervated below the D-8 dermatome. The paretic musculature failed to respond to repeated passive manipulation or to various other stimuli. The superficial and deep reflexes were absent below the level of transection, but the anal sphincter was tonic.

Case 27, W. D., age 20, sustained a bullet wound of the spine on February 19, 1945. X-rays revealed a large metallic fragment in the body of the 12th dorsal vertebra. Laminectomy of D-11, 12, and L-1 on February 21, 1945, revealed a complete transection of the spinal cord at the level of the 12th dorsal vertebra.

The first involuntary movements were noted in the thighs and knees approximately six weeks after cord transection. Muscle activity spread slowly throughout both lower extremities and bilateral withdrawal patterns had developed eight months post-injury. Occasional extensor movements occurred at this time but were not severe until approximately 16 months after injury, by which time they constituted the dominant spasm pattern. Bicycling movements did not appear, although stepping was noted fairly frequently. Weight-bearing on the plantar surfaces was found consistently to provoke extension of trunk and extremities. The frequency of erections was closely related to the vigor and frequency of reflex muscle activity. There were no ejaculations noted.

Neurologic examinations two years after cord transection revealed a mild but dominant extensor spasm pattern; shifting the patient from a sitting to a supine position was adequate stimulus to evoke generalized extension, involving the lower abdomen, hips and lower extremities. Rubbing the thighs or calves elicited little muscle response, but squeezing the thigh musculature provoked ipsilateral and occasionally bilateral extension. Rigidity was never maintained more than 4–5 seconds. There was definite resistance to flexion of the lower extremity at the knee and pelvis, but once this was overcome, the clasp-knife phenomenon could be demonstrated with either limb. There was no extensor thrust.

Nociceptive stimulation of the plantar areas produced jerking withdrawal movements that were quite attentuated, the involved limb never flexing more than 30 degrees at the hips. There was no crossing noted. Midline perineal pinprick evoked bilateral triple-flexor movements. Strong hallux dorsiflexion was present bilaterally.

The superficial abdominal reflexes were absent; the deep were present and 2+ in the lower quadrants. No cremasterics were elicited. Knee jerks were 3+ bilaterally with unsustained clonus. Ankle jerks were 2+ bilaterally and no clonus was elicited. The Babinski responses were marked bilaterally.

DISCUSSION

An unparalleled opportunity for the study of long-surviving patients with traumatic lesions of the spinal cord has been afforded by World War II. Knowledge of the reflex functions of the cord has recently been extended and clarified. Thus, earlier views regarding the physiology of the "automatic" bladder have been re-evaluated (8), and hitherto unknown facts relating to the sensory capacities of the isolated spinal cord have been reported (9).

The classic exposition by Head and Riddoch (2, 3) is the only available detailed analysis of the reflex activities exhibited by chronically spinal men. Since none of their subjects were studied later than a year after injury, it is not surprising that our observations, made on men who had survived complete transection for periods of from 24 to 42 months, lead to conclusions regarding the reflex capacities of the isolated human cord which are quite different from those reached by Head and Riddoch. Factors contributing to the present-day high rate of survival and length of life of paraplegics have been mentioned earlier in this paper. It seems certain that most of the apparent discrepancies between our observations and those of earlier investigators can be explained by the greater duration of life and by the better physical condition of our subjects.

In order to obviate any doubts regarding the nature of their lesions, only those men with complete transection of the spinal cord, verified by surgical exploration, were used in the present study. This necessitated the elimination of numerous patients with "physiological" transections; i.e., subjects who had not been explored but were completely lacking in sensation or voluntary movement below the level of injury.

We have made no attempt to categorize our patients as exhibiting "paraplegia-in-flexion" or "paraplegia-in-extension." In the past, these terms, because they have been poorly defined, have resulted in considerable confusion, rather than clarity. Thus, "paraplegia-in-flexion" has been applied in some instances to patients who exhibit predominant, though poorly sustained, flexor movements, and in other cases to subjects with permanent, extreme, cicatricial contractures. "Paraplegia-in-extension" may refer, depending on the particular

author, to the patient with intermittent extensor movements or to one who exhibits more or less continuous and very marked extensor hypertonia similar to that seen in acute or chronic mesencephalic and bulbospinal animals (10, 11, 12). In this report, detailed analyses of the flexor and extensor movements elicited in each patient have been presented and no effort has been made to classify rigidly their reflex activity.

It is apparent from the case histories (vide supra) that, although marked individual variations occur, there is a striking similarity in the general pattern exhibited by most of the patients. In our experience, the most typical sequence of events following spinal cord transection in man is: 1. Spinal shock, 2. Minimal reflex activity, 3. Flexor spasms, 4. Alternating flexor and extensor spasms, and 5. Predominant extensor spasms. The length of time that different subjects remain in a given stage varies considerably. In general, stage 1 lasts for one to six weeks; stages 2 and 3, six weeks to one year; stage 4 rarely begins prior to four months after injury, and usually is terminated within one year; and stage 5 may appear as early as six months after injury, and may continue indefinitely. Two of our patients did not progress beyond stage 3, and two others remained in stage 4 twenty-four months after transection. The majority of the patients were in stage 5 two years after the lesions were incurred. It is interesting to note that in all our patients reflex activity first appeared at the distal parts of the limbs and spread rostrally, whereas in recovery from a hemiplegia the proximal parts demonstrate earliest recovery, and spread of activity proceeds distally.

It is debatable whether the five patients who failed to exhibit reflex activity of the skeletal musculature below the level of transection were in spinal shock or whether they had suffered not only division of the cord but a lower motor neuron lesion as well. Electrical stimulation of the exposed left sciatic nerve of one of our patients (case 5) evoked no response whatsoever (9). On the other hand, an occasional patient may remain in stage 1 or 2 several months, only to progress rapidly through stages 3, 4, and 5 later. It is evident, therefore, that the presence or absence of gross reflex activity mediated through the isolated cord is of little prognostic value during the first few months in so far as the eventual recovery from spinal shock is concerned.

The cases of Head and Riddoch (2, 3) were strikingly similar to our own before the latter had progressed beyond stage 3. In their studies these investigators make no mention of any observations later than one year after transection. It is of some interest that Dr. Head recorded the following note regarding their patient No. 1, 290 days after injury (2, pp. 295–296):

> "On scratching the sole of either foot, flexion occurred at knee and hip, the ankle dorsiflexed, and the toes went up. The flexor movement reached its height after the brief stimulus was removed, and then the leg slowly straightened. *It was liable to end in extensor spasm.*" (Italics ours).

This type of reflex response is suggestive of that exhibited by our patients in stage 4.

Many of our patients exhibited reflex activities which are practically identical with those manifested by the chronic spinal dog. Sherrington (13) noted that the after-contraction of extensor muscles in a spinal dog shows a rapid, tremulous decline lasting at longest a few seconds, whereas in decerebrate preparations the reflex movements are of rapid onset but subside sluggishly. At least five of our patients, however, demonstrated generalized extensor rigidity, rapid in onset, sustained fully seven to eight seconds, and succeeded by slow "plastic" relaxation. Powerful, sustained extensor thrust in response to broad innocuous pressure on the plantar surface with the hip and knee partially flexed was not a common finding, but could be elicited in a few patients. Some subjects exhibited strong, sustained thrusting movements at the pelvis when the thigh was forcibly flexed at that joint. Certain of the men with high cord lesions were able to stand without mechanical support for as long as one minute before buckling occurred at the knees. Since under these conditions all muscle groups of the lower extremities were simultaneously in contraction, this demonstrates the occurrence of the positive supporting reaction. Such individuals could stand with ease and for prolonged periods in warm water. These observations indicate that spinal standing can occur in men as well as in the dog.

Ipsilateral withdrawal reflexes were commonly accompanied by crossed extension, and the forced passive extension of one limb often led to crossed triple-flexion movements. Lengthening and shortening reactions were present in all patients exhibiting moderately active

extensor spasms, and the clasp-knife phenomenon was frequently demonstrable. In reference to spinal man, it has been stated that, although the knee and ankle jerks recover, they are easily inhibited, and a clonus never develops (5, 6). Vigorous clonus was frequently noted in our patients, and many were greatly disturbed by the rhythmic "jumping" which often occurred in their lower extremities when their plantar surfaces came in contact with the foot-rest of a wheelchair. When severe extensor activity could be provoked the elicitation of patellar and ankle clonus was commonly succeeded by generalized extensor rigidity of the ipsilateral limb. A few men displayed vigorous patellar reflexes despite the finding of a loose Achilles tendon and an absence of toe responses. The reflex responses of spinal men will be subjected to a more thorough analysis in a forthcoming account. It is relevant, perhaps, to mention that the "mass reflex" and bladder facilitation described by Head and Riddoch were not found in our series of chronic spinal men.

Complete erection could be induced by non-nociceptive stimulation of the penis in the majority of patients manifesting reflex activity below the level of cord injury. Noxious stimulation within the genital area resulted invariably in delayed but progressive detumescence. Indisputable evidence of ejaculation was obtained in one patient (R. S.).

The explanation for the occurrence of primary extensor manifestations in these patients is not clear. In our opinion, such reflex responses probably represent the reappearance of primitive and poorly integrated postural activity mediated by the isolated cord. They stand in sharp contrast to the exclusively flexor responses which characterize the early stages of recovery following cord section and which belong to Sherrington's phylogenetically most primitive group of nociceptive reflexes (14). It appears that the functional capacity of the isolated cord, if given sufficient time to recover, is greater than has been assumed. An analogy may be drawn to the earlier views concerning the capacity of mesencephalic and bulbospinal animals. Recently, many additional righting and postural patterns have been demonstrated in these preparations because for the first time it has been possible to maintain them under satisfactory conditions for long periods (12).

The cases reported in this series are not entirely without precedent.

Merritt, Mettler and Putnam (15) mention the occurrence of occasional poorly sustained extensor spasms in patients with complete cord transections. Freeman (16), working with wounded veterans of World War II, has observed instances of extensor spasms exhibited by completely spinal men. Munro, who has probably had more experience with this type of patient than any other recent investigator, does not rely on the presence or absence of reflex activity in the extensor muscles below the level of cord injury, as a criterion of anatomic cord transection (17, 18).

The treatment of spasms of the lower extremities in spinal men deserves mention. Medical therapy has been of little value (19) despite some early encouraging reports on the use of curare. Fortunately, severe spasms of the skeletal musculature can be completely eliminated, in most cases, by anterior rhizotomy (17, 20).

SUMMARY AND CONCLUSIONS

1. The involuntary activity patterns of skeletal muscles innervated below the level of lesion in 27 verified cases of complete spinal cord transection have been studied. In each instance, examination was possible at least two years after division of the cord had occurred. Observations were made on men who had survived complete transection of the cord for periods of from 24 to 42 months. The levels of transection ranged from D-2 through D-12.

2. During the periods of observation two patients exhibited flexor spasms alone; two showed approximately equal flexor and extensor spasms; and eighteen displayed predominant extensor spasms. Five patients were completely flaccid below the level of lesion.

3. The most typical progression of reflex activity following spinal cord transection in this series of patients was:

1. Spinal shock
2. Minimal reflex activity
3. Flexor spasms
4. Alternating flexor and extensor spasms
5. Predominant extensor spasms

The length of time that different subjects remain in a given stage varies considerably. In general, stage 1 lasts for one to six weeks; stages 2 and 3, six weeks to one year; stage 4 rarely begins prior to four

months after injury, and usually is terminated within one year; and stage 5 may appear as early as six months post-injury, and may continue indefinitely.

4. Extensor thrust is not a common finding but can be elicited occasionally in spinal man.

5. "Spinal standing," similar to that seen in animals with transected cords, can occur in spinal man.

6. Sustained patellar and ankle clonus frequently occurs in chronic spinal man.

7. Primary extensor manifestations in chronic spinal man probably represent the reappearance of primitive and poorly integrated postural activity mediated by the isolated cord. It would appear that the functional capacity of the isolated human spinal cord is greater than has been assumed.

8. It is concluded that, though spinal man passes through a period in which flexion reflexes alone are active, he may frequently progress to a stage of activity characterized by predominantly extensor reflexes, amounting in many cases to extensor spasm.

9. Extensor spasm in skeletal muscles, innervated below the level of transection, is not conclusive proof of an incomplete division of the human spinal cord.

10. It is probable that many of the discrepancies between these observations and those of earlier investigators can be explained by the increased duration of life and, secondarily, by the better physical condition of present-day spinal men.

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PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE[1]

VII. Pulmonary Arterial Hypertension in Congenital Heart Disease

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Pulmonary arterial hypertension has been observed in patients with several types of congenital cardiac malformations. Dexter and his associates have observed an increase in pulmonary arterial pressure in patients with ventricular septal defect, with auricular septal defect, and with patent ductus arteriosus (1, 2). Brannon, Weens, and Warren have described a case of atrial septal defect in which catheterization revealed marked elevation of the pulmonary arterial pressure (3). In cases of Eisenmenger's complex and isolated septal defects, similar observations have been described in two previous papers of this series (4, 5).

These reports indicate that pulmonary hypertension can occur in various forms of congenital heart disease. In this laboratory, pulmonary hypertension has been frequently observed during the course of study of a large group of patients with congenital cardiac malformations. This paper presents an analysis of these cases, with an attempt to determine the frequency, the distribution, and the dynamics of pulmonary arterial hypertension.

METHODS

A total of twenty-four patients with pulmonary hypertension, ranging in age from 6 to 46 years, was studied. Only patients in whom the pulmonary artery was catheterized and who had a mean pulmonary arterial pressure of at least 25 mm. of Hg were selected for this report.

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Bloods for analysis from the various parts of the circulatory system were obtained by cardiac catheterization, following the method of Cournand (6) and by puncture of the femoral or brachial artery. Blood gas analyses were carried out in the manometric apparatus of Van Slyke and Neill (7). Arterial and intracardiac pressures were optically recorded by means of a Hamilton manometer (8). In the latter part of this series strain gauge manometers were used. Mean pressures were calculated by planimetric integration of the area under the pressure curve. In four cases (#19, J.W., #21, J.W., #22, P.W., and #24, E.F.) the mean pressure was calculated from the sphygmomanometric readings by adding one-third of the pulse pressure to the diastolic pressure. Respiratory gases were collected in Douglas bags and analyzed in the Haldane apparatus (9). All gas volumes were expressed in terms of dry gas at standard temperature and pressure (STPD). In the latter part of this series, the Pauling oxygen analyzer was used to determine the partial pressure of oxygen. The standard exercise test used in this study has been described in an earlier communication. Its interpretation and significance will be discussed further in a subsequent publication (10).

The formulae used to estimate the various blood flows were discussed in the first paper of this series (11). In Table I the flows are expressed as indices (liters/min./M^2). In the calculation of the work of the heart, Table II, uncorrected values were used. For the sake of clarity, formulae used in the calculation of peripheral and pulmonary resistance and in the estimation of the work of the heart are restated:

Pulmonary and systemic peripheral resistances were calculated by Aperia's formula (12).

$$\text{I. } R = \frac{1.332 \times P}{F}$$

where

R = Resistance (dynes/$cm.^5$/sec.), systemic or pulmonary.
P = Mean blood pressure (mm. of Hg), aorta or pulmonary artery.
F = Flow (liters/sec./M^2), aorta or pulmonary artery.

Starling's formulae were used in the estimations of the work of the ventricles (13). Employing these formulae, values are derived for the

velocity and pressure energy developed by each ventricle. In cases of ventricular septal defect, however, particularly when there is overriding of the aorta, the presence of the shunt precludes the accurate calculation of these energy expenditures. For this reason, comparison of the work of each ventricle with that of a normal ventricle should not be made. However, certain conclusions may be reached by comparing the relationships of the work of the two ventricles of the same heart. To accomplish this, the ratios of velocity energy to total work of the right and left ventricles are compared. The proportion between the ratio $\frac{\text{velocity energy}}{\text{total work}}$ (right ventricle) and the ratio $\frac{\text{velocity energy}}{\text{total work}}$ (left ventricle) may then be compared to that proportion computed for the normal heart. This affords some indication of the work relationship between the ventricles of the abnormal hearts.

II-a Pressure Energy = M.P. × S.D. × D.Hg (Gram-cms.). where

M.P. = Mean Blood Pressure in the pulmonary artery or aorta (cm. of Hg).

S. D. = Systolic Discharge (cc./beat) = $\frac{\text{Blood flow (cc./min.)}}{\text{Pulse rate (beats/min.)}}$

D.Hg = Density of Mercury (13.6).

II-b Velocity Energy = $V_a^2 \times S.D./2g$ (gram-cms.) where

S.D. = Systolic Discharge (cc./beat)

g = Gravity Constant, 980 cm./sec./sec.

$$V_a = \frac{S.\,D.}{Ca \times E.\,T.}$$

and

C_a = Cross sectional area of pulmonic or aortic valvular ring ($cm.^2$).

$$E.\,T. = \text{Systolic Ejection Time (sec.)} = \frac{60/\text{pulse rate}}{8/3}$$

The cross sectional area of the pulmonary valvular ring was assumed to be 5.14 cm.^{2} and of the aortic valvular ring 3.9 cm.^{2} (14). In two patients, (#21, J.W., and #23, P.W.), the measurements secured at post-mortem examination of the patients were applied.

The physiological criteria for the diagnosis of ventricular and auricular septal defect and patent ductus arteriosus have been summarized in a previous paper (15). All patients with coarctation of the aorta fulfilled the clinical criteria for this diagnosis (16), which was confirmed at the time of operation. Of the three patients with partial transposition of the great vessels and overriding of the pulmonary artery, the diagnosis was confirmed in one case (#23, P.W.) at post-mortem examination. The other two patients met the physiological criteria for the diagnosis of this condition (17).

RESULTS

Table I lists the data obtained in twenty-four patients with congenital heart disease and pulmonary arterial hypertension. The patients are grouped according to their cardiac malformation. The sequence in each catagory is determined by the degree of pulmonary hypertension.

Table I shows that thirteen patients had an isolated septal defect, eight of which were ventricular and five auricular. Two patients with patent ductus arteriosus are listed, one with an associated ventricular septal defect. Six patients with coarctation of the aorta are included. Three patients had partial transposition of the great vessels with the aorta arising from the right ventricle and the pulmonary artery overriding the ventricular septum.

The mean pulmonary arterial pressures ranged from 25 to 102 mm. of Hg (Table I). In patients with auricular septal defect, the mean pulmonary pressures were from 25 to 82 mm. of Hg, while the mean pressure in patients with a ventricular septal defect tended to be higher, ranging from 34 to 102 mm. of Hg.

In one patient with a large patent ductus arteriosus (#15, A.T.), the mean pressure was 35 mm. of Hg. In the second patient, where there was an associated ventricular septal defect (#14, H.W.), the mean pulmonary arterial pressure dropped from 73 to 27 mm. of Hg after ligation of the ductus.

TABLE I

Blood Flows, Blood Pressures, and Vascular Resistance in Pulmonary and Systemic Circulations

CASE NO.	DATE	NAME	SEX	AGE	SURFACE / READ METER[3]	PULM. ART. PRESSURE S/D mm. Hg	PULM. ART. PRESSURE Mean mm. Hg	PULMONARY FLOW L/MIN/M[2]	PULMONARY RESISTANCE DYNES/CM[5]/SEC.	FEMORAL ART. PRESSURE S/D mm. Hg	FEMORAL ART. PRESSURE Mean mm. Hg	AORTIC FLOW L/MIN/M[2]	SYSTEMIC RESISTANCE DYNES/CM[5]/SEC.	SHUNT L/MIN/M[2]
				Normal Range		25/10	18	2.0	720	120/80	93	2.0	3720	
						25/10	18	3.0	480	120/80	93	3.0	2480	
						25/10	18	4.0	360	120/80	93	4.0	1860	
Auricular Septal Defect														
1	2/26/48	J.C.	F	29	1.52	40/11	25	4.75	423	85/57	70	3.0	1900	1.75
2	10/28/47	V.E.	F	27	1.18	49/20	38	2.51	1220	142/87	107	1.65	5200	0.86
3	2/24/48	J.L.	M	9	1.17	88/42	62	6.85	726	138/64	75	3.5	1720	5.13
4	9/15/47	G.D.	M	16	1.72	74/47	64	2.62	1920	136/88	103	3.33	2490	0.71*
5	4/2/47	L.G.	M	30	2.0	103/70	82	1.23	5380	100/73	77	4.78	1230	3.55*
Ventricular Septal Defect														
6	3/1/48	J.G.	M	23	1.67	68/9	34	6.35	384	95/83	87	2.78	2500	3.47
7	9/30/47	A.W.	M	9	1.16	41/27	34	3.92	696	155/77	106	3.24	2620	0.68
8	3/30/48	H.P.	M	23	1.56	75/44	59	1.19	3980	128/75	93	1.97	3800	0.78*
9	2/3/48	E.L.	F	29	1.34	92/58	74	1.12	5300	112/62	96	6.6	1160	5.48*
10	12/12/46	V.S.	F	25	1.53	112/64	80	2.71	2340	112/79	95	2.5	3040	0.21
11	3/12/47	B.S.	M	9	0.92		90	2.28	3130		100	2.72	2960	0.44*
12	11/15/46	E.S.	F	19	1.53	122/86	98	2.2	3560	134/82	102	2.62	3120	0.40*
13	4/11/47	H.M.	M	24	1.83	115/90	102	1.91	4200	117/103	108	3.86	2230	1.95*
Patent Ductus Arteriosus														
14	6/16/47	H.W.	F	16	1.26	97/56	73	2.52	895	111/55	100	5.35	1490	2.83
	3/22/48	(postoperative)				48/16	27	3.22	670	120/70	84	1.93	2030	1.19
15	4/13/48	A.T.	F	26	1.45	43/26	35							
Coarctation of the Aorta														
16	3/10/48	D.B.	M	22	1.95	40/6	25	3.85	520	134/62	98	3.85	2020	
17	1/22/47	S.D.	M	45	1.46	44/20	26	2.20	945	137/109	121	2.20	4400	
18	6/26/47	W.D.	M	17	1.59	44/18	30	2.80	860	171/93	135	2.80	4900	
19	1/27/48	J.W.	M	15	1.87		35	2.86	980	180/50Ⓢ	92	2.86	2560	
20	6/20/47	B.C.	F	20	1.62	49/26	35	8.0	350	200/115	162	8.0	1620	
21	6/24/47	J.W.	M	6	0.83	116/87	100	2.34	3420	140/90Ⓢ	102	2.34	3490	
Partial Transposition														
22	2/5/48	H.W.	M	15	1.41	60/46	49	3.94	1120	129/87	100	2.94	2720	
23	1/28/48	P.W.	F	5	0.70	57/45	50	2.3	1740	100/80Ⓢ	87	3.92	1780	
24	5/17/48	E.F.	M	15	1.35	100/91	95	6.65	1140	100/85Ⓢ	90			

* Shunt is from right to left, all other shunts are from left to right.

Ⓢ Sphygmomanometric pressure.

All but one patient with coarctation of the aorta had mild pulmonary arterial hypertension ranging from 25 to 35 mm. of Hg. The one patient (#21, J.W.) with a marked elevation of the mean pressure to 100 mm. of Hg also had congenital mitral stenosis and pulmonary arteriolosclerosis.

Three patients with partial transposition of the great vessels had mean pressures from 49 to 95 mm. of Hg.

The mean systemic blood pressure was elevated in six patients. One patient (#2, V.E.) had an auricular septal defect. Two patients (#7, A.W. and #13, H.M.) had ventricular septal defects. The remainder had hypertension in the upper part of the body associated with coarctation of the aorta.

In three patients with auricular septal defects (#1, J.C., #3, J.L., and #5, L.G.), the mean peripheral arterial pressure was below normal, ranging from 70 to 80 mm. of Hg. In 14 individuals the systemic blood pressure was within normal limits.

Pulmonary artery blood flow ranged from 1.1 to 8.0 liters/min./M^2 (Table I). Significant elevation of the pulmonary blood flow was found in five patients: one with coarctation of the aorta (#20, B.C.); two with auricular (#2, J.C. and #3, J.L.) and one with a ventricular septal defect (#6, J.G.); and one with partial transposition of the great vessels (#24, E.F.). In four patients with isolated septal defects, the pulmonary artery flow was less than 2.0 liters/min./M^2 (#8, H.P., #9, E.L., #13, H.M., and #5, L.G.).

The aortic blood flow, representing the systemic blood flow plus the collateral circulation to the lungs (11), ranged from 1.65 to 8.0 liters/min./M^2. The aortic blood flow was elevated in four patients: one with an auricular septal defect (#5, L.G.); one with a ventricular septal defect (#9, E.L.); one with a patent ductus arteriosus (#14, H.W.); and one with coarctation of the aorta (#20, B.C.). In one patient with patent ductus arteriosus, the aortic blood flow could not be calculated (#15, A.T.). In this case the oxygen content of pulmonary arterial blood equaled the oxygen content of femorial arterial blood, probably as a result of streamlining in the pulmonary artery. The finding of an unusually large ductus at operation suggested that the aortic flow must have been markedly increased. In three patients with isolated septal defects, the aortic flow was less than 2.0 liters/min./M^2 (#2, V.E., #8, H.P., and #14, H.W.).

The left to right intracardiac shunt in patients with isolated septal defects ranged from 0.2 to 5.1 liters/min./M^2. In the remaining patients with isolated septal defects, the shunt was directed toward the left, ranging from 0.4 to 5.5 liters/min./M^2. Large intracardiac shunts in both directions were observed in cases of auricular and ventricular septal defect.

TABLE II

Results Obtained from the Standard Exercise Test

CASE NO.	DATE	NAME	CC. OXYGEN CONSUMED PER LITER VENTILATION	
			Rest	Exercise
2	11/9/47	V. E.	22	24
4	7/17/47	G. D.	18	17.5
5	2/4/47	L. G.	21	46
6		J. G.	21	21
9	5/22/47	E. L.	24	22
	2/3/48		25	26
10	12/12/46	V. S.	21	26
11	2/4/47	B. S.	24	23.5
12	12/11/46	E. S.	25	32
13	12/4/47	H. M.	29	21
	3/4/47		31	24
14	4/24/47	H. W.	34	29
	6/17/47		24	25
22	2/2/48	H. W.	21	23
23	1/29/48	P. W.	17	12
24	3/28/48	E. F.	18	31

The standard exercise test was performed on thirteen patients (Table II). Oxygen consumed per liter ventilation remained approximately constant or rose during exercise in all but three patients. A repeat test on one patient with patent ductus arteriosus showed no change in oxygen consumption from rest to exercise, (# 14, H.W.). Of the two other patients which showed a drop, one had ventricular septal defect (# 13, H.M.), the other had a partial transposition (# 23, P.W.).

DISCUSSION

The variations in the degree of the pulmonary and peripheral vascular resistances in the patients of this series are shown in Table I. It may be seen that in seven patients the pulmonary resistance is within normal range. These include two patients with auricular (#1, J.C., and #3, J.L.); three patients with ventricular septal defect (#7, J.G., #8, A.W., and #14, H.W.); and two patients with coarctation of the aorta (#16, D.B. and #20, B.C.). In all others the pulmonary resistance is elevated, ranging from 860 to 5380 dynes/cm.^{5}/sec.

The systemic resistance is increased in two patients with coarctation of the aorta (#17, S.D. and #18, W.D.), and in one with an auricular septal defect (#2, V.E.). It should be pointed out, however, that a large part of the total systemic resistance in patients with coarctation of the aorta is probably due to the resistance of the stenosis and collateral blood vessels while the peripheral arteriolar resistance is within normal range (18). In six instances pulmonary resistance exceeds that in the systemic circulation. This group includes a patient with an auricular (#5, L.G.) and five patients with ventricular septal defect (#8, H.P., #9, E.L., #11, B.S., #12, E.S., and #13, H.M.).

The presence of increased pulmonary vascular resistance is further reflected in the results secured from calculation of the work of the heart (Table III). The proportion of the ratio $\frac{\text{velocity energy}}{\text{total work}}$ (right heart) as compared to this ratio of the left ranges from 0.023/1 to 9.2/1. In the normal the proportion of these ratios is about 3/1. Only one patient, (#6, J.G.), has a significant elevation of this proportion to 9.2/1. This patient has a large pulmonary flow in the presence of mild hypertension. In ten cases the proportion is within normal range. In the remainder it is markedly reduced, due to an increase in the pulmonary resistance (Table I).

An elevation of the mean pulmonary artery pressure can be produced by one or a combination of three mechanisms. These are: increase in the pulmonary arterial flow in the presence of a fixed pulmonary resistance; second, an increase in the pulmonary vein pressure because of impaired drainage into or through the left side of the heart; and, finally, an increase in the peripheral pulmonary arteriolar resistance.

TABLE III

The Work of the Heart in Cases with Pulmonary Hypertension

CASE NO.	NAME	RIGHT HEART			LEFT HEART			RATIO Rt. vel./Rt. work / Lt. vel./Lt. work
		Velocity energy (gram-cm.)	Total work (gram-cm.)	Velocity energy / Total work × 100	Velocity energy (gram-cm.)	Total work (gram-cm.)	Velocity energy / Total work × 100	
Normal*		46	1496	3.1	80.0	7580	1.04	3.0
1	J. C.	134	2427	5.5	56.0	4056	1.4	3.92
2	V. E.	13	1943	0.66	6.0	3496	0.17	3.83
3	J. L.	182	6482	2.8	24.5	3935	0.62	4.5
4	G. D.	34	3954	0.88	126.0	8136	1.55	0.57
5	L. G.	7.5	3668	0.21	1050.0	14250	7.4	0.28
6	J. G.	685	6395	12.0	73.5	5824	1.3	9.2
7	A. W.	40	2310	1.7	38.0	5838	0.66	2.8
8	H. P.	3.1	1863	0.17	24.0	4854	0.49	0.38
9	E. L.	1.2	1429	0.09	442.0	11342	3.9	0.023
10	V. S.	31	5031	0.61	70.0	6570	1.06	0.58
11	B. S.	4.3	3064	0.14	13.0	4133	0.30	0.47
12	E. S.	15	4815	0.31	47.0	6197	0.76	0.41
13	H. M.	21	6771	0.31	316.0	14716	2.1	0.15
14	H. W.	17	4467	0.39	286.0	13386	2.2	0.18
	post-op.	35	2075	1.7	13.0	3893	0.33	5.1
16	D. B.	155	2785	5.4	275.0	10275	2.7	2.0
17	S. D.	13	1203	1.05	22.0	5572	0.39	2.7
18	W. D.	45	2345	1.9	134.0	10454	1.28	1.47
19	J. W.	62	2765	2.2	107.0	7207	1.5	1.47
20	B. C.	575	5965	9.6	1200.0	26100	4.85	1.98
21	J. W.	7	2087	0.33	14.0	2144	0.67	0.5
22	H. W.	84	3909	2.2	62.0	5952	1.04	2.11
23	P. W.	3.9	689	0.55	137.0	2167	6.4	0.086
24	E. F.	272	11272	2.5				

* C.O. = 4500, Rate 75.
Mean P.A. Pressure 18 mm. Hg.
Mean Aortic Pressure 93 mm. Hg.

As an example of the first mechanism, elevation of the mean pulmonary pressure in the presence of an abnormally high pulmonary flow, two cases with septal defect may be cited (#1, J.C. and #6, J.G.). Both have mild pulmonary arterial hypertension in the presence of large pulmonary blood flow.

It seems possible that the increase in mean pulmonary pressure observed in these patients is evidence that the limit of the capacity of the pulmonary bed has been reached. Normally, as shown by Hamilton (19) Cournand (20), Riley et al (21), Levy and Blalock (22), and Hickman and Cargill (23), the capacity of the pulmonary vascular bed is sufficient to accommodate a large increase in the circulating blood volume without an elevation of the pulmonary arterial pressure. An alternative, that the blood flow exceeds the functional capacity of the left auricle, must also be considered in these cases. However, without measurements of the left auricular pressures, the role of this mechanism cannot be evaluated.

The second mechanism in the production of elevated pulmonary resistance, an increase in left auricular pressure, is illustrated in patient #21, J.W., (Table III). Post-mortem examination in this case revealed a severe degree of congenital mitral stenosis, mild arteriolosclerotic changes of the pulmonary vessels, and coarctation of the aorta.

The third mechanism causing pulmonary hypertension, an increase in peripheral arterial pulmonary resistance, is illustrated by the findings in several patients. As examples, patients #5, L.G. and #9, E.L., (Table I), show high pulmonary pressures, low pulmonary blood, flows, and markedly elevated pulmonary resistances. In both patients there is present a very large overall right to left shunt (Table I).

The exact nature of the cause of this increased pulmonary resistances cannot be stated. Arteriolosclerotic changes in the pulmonary vascular bed have been reported in six different congenital malformations of the heart: auricular (24) and ventricular (25) septal defects, patent ductus arteriosus proximal to a coarctation of the aorta (26), Eisenmenger's complex (27), partial transposition (17), (case #23, P.W.) and congenital mitral stenosis with coarctation of the aorta, (case #21 J.W.). (Table I). It is conceivable that similar anatomical changes are responsible for the increased resistance observed in many cases of congenital heart disease.

On the other hand, the possibility must be considered that functional mechanisms may be responsible for a reduction of the cross-sectional area of the pulmonary bed. It is possible that the results of the exercise test afford a means for evaluating the role of these mechanisms. A rise in oxygen consumption per liter of ventilation with exercise may be interpreted as evidence that the pulmonary blood flow can increase sufficiently to take care of the respiratory demands of the standard exercise test. The opinion may be ventured that a rise in oxygen consumed per liter of ventilation, as observed in five of six patients with marked increase in the pulmonary resistance, is more in line with functional rather than anatomical changes in the pulmonary vessels.

SUMMARY

The physiological data collected on 24 patients with congenital heart disease with varying degrees of pulmonary hypertension have been presented. The patients include those with auricular and ventricular septal defect, patent ductus arteriosus, coarctation of the aorta, and partial transposition of the great vessels.

Three mechanisms have been proposed which could have produced pulmonary hypertension in these patients:

1. Increase in pulmonary blood flow in the presence of fixed pulmonary resistance;
2. Increase in the pulmonary vein pressure; and
3. Reduction of the cross-sectional area of the pulmonary vascular bed.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Brief Psychotherapy. By BERTRAND S. FROHMAN. 265 pp. $4.00. *Lea & Febiger, Philadelphia, Pennsylvania,* 1948.

A book entitled "Brief Psychotherapy" is tempting bait to a physician when offered as an aid in detecting and managing the functional disturbances he finds among his patients. A readable and competent presentation of the clinical aspects of the neuroses has been added to the literature without adding anything to the literature. The reviewer might take exception to various statements and concepts presented, but they are not too damaging. However, the book can be of little help to the practitioner and may well be dangerous. The techniques of "Brief Psychotherapy" described are short-cuts which may be feasible for an experienced therapist. The author, for example, stresses the use of the active analytic technique of Stekel which requires unusual competence in dream interpretation. Even simple dream interpretation is best left to the experienced psychotherapist. Similarly, hypnosis, narcosynthesis, shock therapies, the use of general semantics (Korzybski), have no place in the armamentarium of a practitioner of general medicine. The book has some value as a means of informing physicians how some psychiatrists may go about helping patients, but even here the book may mislead by making some difficult problems sound relatively simple.

T. L.

Clinical Diagnosis by Laboratory Methods. 11th ed. By JAMES C. TODD, ARTHUR H. SANFORD, and GEORGE G. STILWELL. Illus. 954 pp. $7.50. *W. B. Saunders Company, Philadelphia, Pennsylvania,* 1948.

This new edition compares favorably with the previous volumes which have made this text a favorite among students and laboratory workers. The illustrations are profuse and excellent. Techniques are clearly presented. The authors have undertaken to cover an almost impossibly comprehensive material in a volume of moderate size. They have succeeded in getting the essence of most of the clinically important methods into the book, but students of the individual sciences may quarrel with the selection, and interpretation of some of the tests. On the whole, however, this is a remarkably successful attempt to compress the whole of laboratory medicine into a readily usable form.

J. A. L., Jr.

Epithelia of Woman's Reproductive Organs, The. By GEORGE N. PAPANICOLAOU, HERBERT F. TRAUT, and ANDREW A. MARCHETTI. Illus. 53 pp. $10.00. *The Commonwealth Fund, New York, New York,* 1948.

This short monograph is based on a review of the literature and a complete study of a large series of human organs by the authors. Their discussion of the histology and cyclic changes observed in the ovary, tubes, uterus and cervix compares closely to that given in standard texts of gynecology. However, their thorough study and analysis of the material, with a review of the existing literature, makes the monograph a valuable, complete and concise reference.

The great emphasis on the vaginal cyclic changes and cell smear techniques by Dr. Papanicolaou clearly summarizes for the reader the exhaustive work of many years by the master in the field. Most of the many illustrations are in color, large and well chosen. The exceptional excellence of color reproduction and clarity form a major point of praise for this book. It is a beautiful color atlas of the histology of the female reproductive tract during the different physiologic periods.

M. B.

Essentials of Public Health. By WILLIAM P. SHEPARD, with the collaboration of CHARLES E. SMITH, RODNEY R. BEARD, and LEON B. REYNOLDS. Illus. 600 pp. $5.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania,* 1948.

This volume is one of a series of summaries put out by the J. B. Lippincott Company. It is an excellent and very complete summary of the broad field of Public Health and Preventive Medicine.

The senior author, Dr. William P. Shepard, has long been associated with the general Public Health movement and has, for many years, participated in the teaching of Public Health and Preventive Medicine at the Stanford University School of Medicine. He is ably assisted by the co-authors, Charles Edward Smith, Rodney Ralph Beard, and Leon Benedict Reynolds, all of whom have had wide experience in various phases of Public Health and Preventive Medicine activities.

The volume was designed to meet the needs, apparently, of teaching of Preventive Medicine and Public Health to medical students. There is, if anything, more than adequate coverage of the traditional environmental control activities dealing with water purification, sewage disposal, and food control, which is almost traditionally dull reading for medical students.

The sections on Communicable Disease Control and Public Health Activities are unusually complete and well written. These sections, particularly, emphasize the rôle of the practicing physician in the prevention of disease. Factual material contained in the text is accurate and well presented. The frequent use of charts and tables simplifies the reader's understanding of the material.

The medical students and the busy practicing physician should find the volume a handy, brief reference instrument, and the bibliography of each section is sufficiently complete to give him source material for further study. This volume might well be on the shelf of every practicing physician.

E. L. S.

Hemolysis and Related Phenomena. By ERIC Ponder. Illus. 398 pp. $10.00. *Grune & Stratton, Inc., New York 16, New York,* 1948.

Few biological systems have been subjected to so intensive investigation by so many techniques, and by workers in such a wide variety of diverse fields, as the mammalian erythrocyte. The apparent simplicity of this cell, and the ease with which it can be manipulated and observed in experimental studies, have attracted the interest of many laboratories during the past five decades. In "Hemolysis and Related Phenomena", Ponder has brought together much of the accumulated information concerning the red cell, emphasizing throughout his presentation the extraordinary complexity of this apparently simple structure, and the problems regarding its nature which remain unsolved.

The book would seem at first consideration to be of interest primarily to those engaged in the specialty of Hematology. But this is certainly less than the case. The methods and observations described in this compendium will be of interest to workers in many other fields bearing upon the general problem of cellular form and function. The student and physician will use the book as an authoritative reference work for questions which arise in connection with red cell disease, and even though many of the answers will seem theoretical and hardly applicable to practice, they are at least answers. And the general reader, whatever his field, will find considerable pleasure in the reading of this book. The language of Ponder is precise, elegant, and often delightful, and throughout the book one is aware of the well tempered alloy of enthusiasm and skepticism on which it is based.

The book is literally packed with facts, many of which are attended by excellent charts and figures, and there are over five hundred references to primary sources. Chapter I consists of an introductory essay, summarizing the aims and scope of the monograph. Chapters II and III deal with the shape of the red cell, and with the factors involved in changes in shape, particularly with regard to the disc-sphere transformation. Chapter IV is concerned with the cytochemistry and architecture of the cell, and here are discussed the constituents of the red cell, the composition and arrangement of surface structures, and the probable mosaic complexity of supporting tissue and entrapped material which comprise the interior of the cell. The sickling phenomenon is described in considerable detail. Chapters V, VI, and VII deal with the kinetics of hemolysis and the numerous factors which influence hemolysis. The mechanisms which may be implicated in the *in vivo* destruction of the red cells are taken up in the last chapter, and the possible rôle played by these mechanisms in certain hemolytic diseases is discussed.

There are four brief appendices, dealing with the red cells of the *Camelidae*, the nucleated red cells of the lower vertebrates, the technic of red cell counting, and the metabolism of red cells. The latter appendix contains a great deal of valuable material in concentrated form, and this reviewer would be glad to see it amplified in a future edition and elevated to the status of a chapter.

Lest it be thought that the scope of this book is restricted to a single subject with which it deals, or that the author's preoccupation with this subject is an instance of extreme specialization, it is well to reproduce the following from the

author's introduction. "I have been told that I tend to speak of the red cell as if it were a microcosm, and as if an understanding of its nature and properties would include an understanding of nearly everything else in the cellular world. To some extent this is true, for there is scarcely a fundamental problem in General Physiology which does not have a relation, of one kind or another, to the problems which have arisen in connection with the erythrocyte." A book which embarks with such a viewpoint, and is at the same time the work of a selective and meticulous mind, is likely to be a good book indeed. This one is.

L. T.

History of the American Medical Association 1847–1947. By MORRIS FISHBEIN. Illus. 1226 pp. $10.00. *W. B. Saunders Company, Philadelphia, Pennsylvania*, 1947.

In 1947 the American Medical Association celebrated its hundredth anniversary. It was on this occasion that the Board of Trustees of the Association offered the present volume "as a record of its founder, its founding, its ideals and its motivations and the extent to which these have been accomplished over a period of one hundred years" (p. v).

It may not be without interest to compare the primary motivations which led to the founding of the American Medical Association and that of its older cousin, the British Medical Association. The latter came into existence in 1832 as the "Provincial Medical and Surgical Association" (it assumed its present name in 1856 only) upon the initiative of Doctor (later *Sir*) Charles Hastings. He conceived of its chief goal as "the diffusion and increase of Medical Knowledge in every department of science and practice."[1] Only as a final point did the original prospectus list "Maintenance of the Honour and Respectability of the Profession generally, in the Provinces" etc.[2] However, the question of medical education and licensure soon became of great importance and from the late thirties engaged the active interest of the Association.[3] Now when Nathan Smith Davis in 1845 suggested the convocation of a National Medical Convention in this country, it was just "the elevation of the standard of medical education in the United States" that was the prime object.[4] When the organizational meeting was held in 1846, it took up this desideratum, but also enlarged it by the demand for a uniform code of medical ethics and by appointing committees which were to branch out into more scientific aspects.[5] On this basis, the A. M. A. came into life in 1847. The anarchic state of the medical profession in this country as well as in Great Britain, and the stimulus of an age of developing science led the medical associations of the two countries to pursue a similar direction from different starting points.

[1] *History of the British Medical Association 1832–1932*, compiled by Ernest Muirhead Little, London, British Medical Association, n.d., p. 19.

[2] *Ibid.*, p. 21.

[3] *Ibid.*, p. 61.

[4] Fishbein, *op. cit.*, p. 22.

[5] *Ibid.*, p. 25 f.

Since 1847 some of the main goals for which the A. M. A. had been striving have been reached, but many new tasks have been imposed and new problems, no less controversial than those of a hundred years ago, have to be faced. Dr. Fishbein's chronological account, the biographies of the presidents, the sketches outlining the activities of the various councils, bureaus, sections, etc., and of the organs of publication give a picture of the past and present of what is probably the largest medical organization in the world. This picture is not only instructive, but because of the official character of the book it also represents a record that will have to be consulted by all those interested in their profession.

O. T.

Hospital Trends and Developments, 1940–1946. By ARTHUR C. BACKMEYER and GERHARD HARTMAN. 819 pp. $5.50. *The Commonwealth Fund, New York, New York*, 1948.

In their earlier work, "The Hospital in Modern Society", the editors covered hospital literature up to 1940. The 148 papers in their present volume represent their choice of the best papers between 1940 and 1946 and cover a wide variety of subjects of importance to both hospital administrator and physician. A comparatively small number of the papers are drawn from the study of more than one hospital, and one can see how desirable studies comparing the methods of one with those of another would be.

C. W. C.

Intracranial Tumors. 2nd ed. By PERCIVAL BAILEY. Illus. 478 pp. $10.50. *Charles C. Thomas, Springfield, Illinois*, 1948.

The second edition of this classic on brain tumors should be received as enthusiastically as the first edition. A few alterations have been made in the text of this edition to incorporate recent advances in the neurological sciences, but the main thesis, based on the pathological aspects of intracranial tumors, remains unchanged. A series of plates illustrating roentgenographic findings is a welcome addition to the book.

Not only students but general practitioners will find this a valuable, instructive and entertaining monograph on the triumphs and limitations of neurological surgery in a field which has advanced so rapidly in the past two decades.

A. E. W.

Manual of Clinical Therapeutics, A, 2nd ed. By WINDSOR C. CUTTING. Illus. 712 pp. $5.00. *W. B. Saunders Company, Philadelphia, Pennsylvania*, 1948.

This book is exactly what the title states—practical therapeutics in compact form. The first two chapters deal with general problems in therapy, and the next eleven with the treatment of various infections. The remainder is divided according to disease categories, first of a general character such as nutritional and endocrine diseases, and then of diseases of the specific systems. Finally there are

nine appendices full of useful information on bedside procedures, physiotherapy, diets and so on.

The author intends the book for use by those who may be confronted by therapeutic problems unfamiliar to them. He fulfills this purpose admirably, and throughout the recommended therapies are quite in line with modern formulations. The only criticism is directed not at the content but at the form. A practical manual such as this is divorced from concepts of disease pathogenesis and of the fate of drugs in the body. It is only by means of an accurate analysis of these factors that the therapist will be able to treat the complex situations so often found at the bedside. This book therefore is recommended to those who wish to know how to treat a patient rather than why such a treatment is necessary.

C. G. Z.

Pathology of Nutritional Disease, The. By RICHARD FOLLIS, JR. Illus. 291 pp. $6.75. *Charles C. Thomas, Springfield, Illinois*, 1947.

This book is just what it purports to be, a compendium of available information on the pathological anatomy of experimentally induced deficiency diseases. The subject matter is divided into sections on (1) deficiencies of essential elements such as calcium, phosphorus, potassium, magnesium, copper, etc.; (2) the essential. amino acids; (3) fat and water soluble vitamins; and (4) the essential fatty acids In the general discussion and summing up of the dietary deficiencies experimentally induced, the author is at pains to emphasize that the facts submitted cannot be directly translated to clinical problems.

The subject matter is clearly treated by the author who has long been active in the field and a prominent contributor. Especially excellent are the treatises on the pathology of rickets and scurvy.

J. E. H.

Textbook of Bacteriology. 9th ed. By HANS ZINSSER. Revised by DAVID T. SMITH, DONALD S. MARTIN, ET AL. Illus. 992 pp. $10.00. *Appleton-Century-Crofts, Inc., New York 1, New York*, 1948.

This ninth edition of the "Textbook of Bacteriology", which in more recent editions had been written by Zinsser and Stanhope Bayne-Jones, is a standard reference and teaching text in many medical schools throughout the country. Now it has been thoroughly rewritten and revised by Drs. David T. Smith and Donald Martin and associates at Duke University Medical School. A great deal of new material has been added, and in many cases the most recent references are listed and the work discussed. A large number of electron micrographs is a new and welcome feature in the section on viruses. However, many of the old illustrations should be done over because of poor reproduction in the present edition.

A number of annoying slips or omissions have been noticed throughout the virus section by this reviewer. Panum's classic account of the spread of measles in an immune population does not refer to the South Sea Islands but to the Faroe

Islands, north of Europe. The production of encephalomyelitis similar to that following vaccination, by the use of Freund's adjuvant technique, is not mentioned. The discussion of the "interference phenomenon" completely ignores the basic work of Magrassi and Hallauer which was done and fully published before 1940. The complete separation of the virus hepatitis complex into (1) epidemic hepatitis, and (2) homologous serum jaundice, a disease "discovered during World War II", is not warranted by the available facts. Even those who propose some strain differences as basic to the different methods of spread say only "There are probably several forms of viral infections of the liver which are variants of one general group."[1]

In general, this edition represents a much needed but an imperfect revision of a standard textbook.

F. B. B.

Textbook of Gynecology. 3rd ed. By EMIL NOVAK. Illus. 742 pp. $8.00. *Williams & Wilkins Company, Baltimore, Maryland*, 1948.

This textbook, which includes the fundamentals of gynecology and female urology, stresses the pathological and endocrinological aspects of the subject. The author has omitted descriptions of operative procedures and has concentrated his efforts on the diagnostic procedures and medical treatment of gynecological disorders. The author has added many new and excellent photographs and photomicrographs in the present edition. Ever changing endocrine concepts and therapy have also been brought up to date.

J. H. L.

Topics in Physical Chemistry. By WILLIAM MANSFIELD CLARK. Illus. 738 pp. $10.00. *The Williams & Wilkins Co., Baltimore, Maryland*, 1948.

This is a superb book, unique in its combination of conciseness and breadth of coverage, brimming with useful information in a usable form. The reviewer's only criticism is of the title, which is much too vague and dry for this lively opus, and which through fear and prejudice may discourage some medical readers from venturing into this fascinating exposition of what makes the body (and a lot of the doctor's instruments) tick.

There is an unusually complete coverage of the principles of chemistry and physics applicable to biological systems and to measuring devices used by the biological scientist. The explanations move along briskly, with a minimum of mathematical derivation, but just enough for clarity. Limiting laws are presented as such, avoiding the frustration of finding at the end of the chapter that the results cannot be applied to existing systems. There is no pomposity of presentation, as the author, with characteristic dry humor, points out the frailties of the "laws" or their misapplications.

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[1] Havens, W. P. and Paul, J. R. in Rivers' "Viral and Rickettsial Infections of Man", 1948.

Each topic is chosen not only for its intrinsic value but for its applicability, and the theoretical expositions are heavily outweighed by the mass of useful applications. Every type of instrument in conventional clinical and research use in biochemical laboratories is considered, briefly but thoughtfully, in terms of what makes it work, how to use it, and what it can be expected to do. Although the application of physical chemical principles to the complex systems of the body is often difficult, there are repeated and well-chosen illustrations of each principle, without visible signs of strain of either the law or the biological facts.

This book can be strongly recommended to every student of the biological and medical sciences as a stimulating and authoritative text or reference source.

J. A. L., Jr.

Tuberculosis. By FRANCIS M. POTTENGER. Illus. 597 pp. $12.00. *C. V. Mosby Company, St. Louis, Missouri,* 1948.

This book is an important contribution to the study of tuberculosis, for it is based on the author's wide experience with the disease over a period of nearly fifty years. The careful compilation of data on the patients in the sanatorium whose progress is followed over a period of years justifies Dr. Pottenger's optimistic viewpoint, as he demonstrates the remarkable tendency of the disease to heal spontaneously if diagnosed early and handled well. The conservative therapy which aids in this healing is aimed at building up the patient's resistance from every standpoint while the reactions of immunity take place.

In the chapter on the pathogenesis of tuberculosis the author's discussion does not seem entirely clear in regard to immunity, hypersensitivity, etc. The latter is considered an important part of the protective mechanism, but the evidence presented in support of this belief does not seem adequate for proof, and the difficult problem of the relationship between specific immunity and hypersensitivity in the clinical picture of tuberculosis is not very clearly defined.

The anatomical variations in the thorax at different ages are described and correlated with the tendency for the site of reinfection to shift to the apex, mainly on the basis of a local reduction of blood supply. The importance of this factor is based primarily on two presumptions: that the bacilli are carried to the site of reinfection by the blood stream, and that their source is endogenous rather than exogenous. While either of these presumptions may be correct, neither of them is easily proven and the author's reasons for favoring the "endogenous" theory are not entirely convincing.

Much space is devoted to a detailed consideration of the symptomatic and structural changes produced by pulmonary tuberculosis on various other systems of the body through the mediation of nerve reflexes. Many of these effects he feels are of importance from a diagnostic standpoint, as he finds he can suspect and locate tuberculous lesions in the lungs by observation and palpation of localized alterations in the overlying muscles. While it is interesting to know that these numerous "reflex" effects may be found in pulmonary tuberculosis, one wonders

if their importance in the pathogenesis and diagnosis of the disease may not be unduly emphasized.

The indications for the various forms of collapse therapy are outlined, with pertinent discussion of their limitations and dangers. Tuberculin is advocated as an additional therapeutic aid in pulmonary tuberculosis—a view that may be questioned by many other students of the disease. At the end there is an excellent summary of the present status of the use of B.C.G. Vaccine, which Dr. Pottenger shows is proving to be both safe and effective.

The book on the whole contains much valuable information on pulmonary tuberculosis, and there are many well-reproduced photographs of chest X-rays to illustrate the points that are made. Much of it seems repetitious, however, and several of the chapters could be shortened drastically without detracting too much from its fundamental value.

A. M. F.

Vascular Disorders of the Limbs. 2nd ed. By SIR THOMAS LEWIS. 118 pp. $2.25. *The Macmillan Company, New York, New York,* 1946.

In a short monograph of 118 pages entitled "Vascular Disorders of The Limbs," Sir Thomas Lewis has sought to bring up to date advances made especially during the ten years preceding the late war relative to disorders of the circulation of the limbs.

The work is written for students and practitioners, so description has been confined to methods of diagnosis which they can employ themselves. At the same time enough is incorporated to insure recognition and adequate management of the different conditions.

The first chapter is called "The Function and Control of the Circulation and Its Testing." Lewis states that three kinds of tests are used in examining the vessesl of a limb according to whether they explore (1) the rate of blood flow, (2) the state of various vessels and especially their capacity to dilate, and (3) the intactness or otherwise of the vasoconstrictor nerves.

The description and interpretation of the varieties of skin color add much to a subject so commonly misunderstood.

In commenting on circulatory arrest, the statement is made that the death of muscle fibers is probably assured when in the warm limb they are deprived of blood from six to eight hours, and their death results in a replacement fibrosis; that nerves recover after being ischemic for twelve or even twenty hours; that blistering of the skin occurs after six to twelve hours of ischemia, and necrosis of the skin after from twenty-four to forty-eight hours; and that the cooler the limb during ischemia, the longer the survival time. In this connection, it is of surgical importance to note that collateral arteries dilate in common with arteries generally when sympathetic tone is lost; thus sympathetic section encourages the return of blood to the ischemic tissues.

It is also of surgical importance to note that in the treatment of embolism of

main arteries, if operation is deemed advisable, the sooner it is done the better; the chances of success rapidly decrease after twelve hours, and are almost gone after forty-eight hours have elapsed.

An excellent short dissertation on intermittent claudication stresses the points that the cause of the pain is an obstacle to the free passage of blood to the affected limb and that this type of pain is the same as that resulting when normal muscles are made to work with the circulation completely arrested. Then follow short chapters on arteriosclerosis, thromboangiitis obliterans, vasoconstriction in general, and Raynaud's disease.

In discussing vasoconstriction, Lewis spends much of this book in furnishing his evidence that the traditional view, which attributes much of peripheral vascular disease to a vasospastic cause, is based on inadequate proof, and that attention should not be focused upon the nervous system but upon the blood vessels themselves.

Unusual types of gangrene are then discussed, then vasodilatation, and finally vascular disorders in diseases of the nervous system.

The whole treatise is written in Lewis' customary clear, simple, authoritative fashion. One wonders at times, however, why he takes such pains to belabor the point continuously that local arterial changes such as minute thromboses are the cause of practically all peripheral vascular disease to the exclusion of primary vasospastic factors. Surgical interference with the sympathetic nerve control has given such unquestioned proof of the importance of the spastic nature of so many of these maladies. With long continued spasm, thromboses may occur as secondary to this partial or complete occlusion of the small blood vessels.

I. R. T.

BOOKS RECEIVED FOR REVIEW

A-B-C's of Sulfonamide and Antibiotic Therapy. By PERRIN H. LONG. 231 pp. $3.50. *W. B. Saunders Company, Philadelphia, Pennsylvania,* 1948.

A Way to Natural Childbirth. By HELEN HEARDMAN. Illus. 124 pp. 7/6 net. *E. & S. Livingstone, Ltd., Edinburgh,* 1948.

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Clinical Roentgenology of the Digestive Tract. 3rd ed. By MAURICE FELDMAN. Illus. 901 pp. $8.00. *The Williams and Wilkins Company, Baltimore, Maryland,* 1948.

Detailed Atlas of the Head and Neck. By RAYMOND C. TRUEX AND CARL E. KELLNER. Illus. 162 pp. $15.00. *Oxford University Press, New York, New York,* 1948.

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Racial Variations in Immunity to Syphilis. A Study of the Disease in the Chinese, White, and Negro Races. By CHESTER N. FRAZIER AND LI HUNG-CHIUNG. 122 pp. $2.50. *University of Chicago Press, Chicago, Illinois,* 1948.

Textbook of Bacteriology. 9th ed. By HANS ZINSSER. Revised by DAVID T. SMITH, DONALD S. MARTIN, ET AL. Illus. 992 pp. $10.00. *Appleton-Century-Crofts, Inc., New York 1, New York,* 1948.

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